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BASAL METABOLIC RATES AND THEIR RELATION TO END-RESULTS IN THYROID DISEASE

A STATISTICAL STUDY

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The purpose of this paper is to present a statistical study of results from the basal metabolism laboratory of the Lahey Clinic, as well as to attempt to correlate certain phases in the diagnosis and therapeutic end-results in thyroid disease to the rate of basal metabolism.

The material comprises the results of 5,200 consecutive tests in 1,675 patients, all of whom were primarily referred to the metabolism laboratory either for an estimation of the severity of thyroid disease when the diagnosis was clinically obvious, or for aid in diagnosis when the clinical picture was obscure.

The basal metabolic rate, when correctly estimated and interpreted, is of undisputed value for both these purposes in the thyroid clinic of today.

In the discussion of results, the cases are divided into two large groups, those in which operation was performed and those in which operation was not done. Of these 1,675 patients, 1,258 patients were operated on, in our clinic, with the following diagnoses: Primary hyperthyroidism, 533 cases (2,786 tests); adenomas (single, multiple, multiple colloid, cystic) with secondary hyperthyroidism, 320 cases (923 tests); benign tumors of thyroid without hyperthyroidism, 390 cases (822 tests), and malignancy of thyroid, fifteen cases (twenty-two tests).

The percentage incidence, therefore, of these forms of thyroid disease, as they appear in the clinic, is as follows: Primary hyperthyroidism, 42.4 per cent.; secondary hyperthyroidism, 25.4 per cent.; tumors of thyroid without hyperthyroidism, 31 per cent., and malignancy of thyroid,[1] 1.2 per cent.

In the clinical group of primary hyperthyroidism, all but nine of the 533 cases showed an increased basal metabolic rate. In these nine cases, 1.6 per cent. of the group, operations were performed in spite of a normal metabolic rate because of a definite history and signs of hyper-

1. The actual incidence of thyroid malignancy, in the clinic, is somewhat larger, as several of the carcinoma cases were not referred to the metabolism laboratory.

thyroidism with remissions. In these cases, an exception was made to our usual routine of awaiting a subsequent exacerbation of the disease because the clinical picture was so definite and because the convenience of the patient made operation at the time seem expedient. Subsequent clinical improvement justified this procedure, and in only one case was there a postoperative fall of the basal metabolic rate to a point below the normal limit.

The remaining 98.4 per cent. of this group of primary hyperthyroidism (524 cases), showed preoperative rates in the following percentage range given in Table 1.

Our study of the clinical data and their relationship to the metabolic data, in this series of primary hyperthyroidism cases, will be based on this grouping according to the level of the basal metabolic rate, and the ten groups of cases, as divided thus, will be used for further comparisons.

TABLE 1.—*Preoperative Basal Metabolic Rate in Five Hundred and Twenty-Four Cases of Primary Hyperthyroidism*

Rate	Number of Cases	Per Cent.
+ 15 to + 19	7	1.3
+ 20 to + 29	32	6.1
+ 30 to + 39	70	13.3
+ 40 to + 49	75	14.3
+ 50 to + 59	92	17.5
+ 60 to + 69	90	17.1
+ 70 to + 79	70	13.3
+ 80 to + 89	40	7.6
+ 90 to + 99	28	5.3
+100 to +120	20	3.8

The table of percentage range of preoperative rates shows that the highest incidence of cases falls in the groups whose rates are between + 50 and + 69. Thirty-four and six-tenths per cent. of all the cases show a preoperative rate within these limits. In cases in which the patients had hospital rest before operation, the rates determined after the rest are used, as there is frequently a considerable drop in the metabolic rate from several days' rest in bed. In those cases treated preoperatively with rest and Lugol's solution, the rate determined by at least two tests before the beginning of treatment is used. These cases will be discussed in a later paper.

The ages of the patients in the primary hyperthyroidism group, when first seen in the clinic, ranged from 16 to 69 years. The previous duration of the disease, as evidenced by the history of symptoms, varied from two months to two years. Table 2 shows the relationship of age to preoperative basal metabolic rate in a series of 493 cases.

In this group of cases of primary hyperthyroidism, a multiple stage operation is frequently practiced. The various stages used in the operative procedure are as follows:

One-Stage.—Subtotal thyroidectomy (or in recurrent cases with involvement of only one lobe, one subtotal hemithyroidectomy).

Two-Stage.—Double superior pole ligation and subtotal thyroidectomy; single pole ligation and subtotal thyroidectomy; elevation of the skin flap and a subtotal thyroidectomy, and two subtotal hemithyroidectomies.

Three-Stage.—One double ligation and two subtotal hemithyroidectomies; one single pole ligation and two subtotal hemithyroidectomies; two single ligations and a subtotal thyroidectomy; one double or single

TABLE 2.—*Preoperative Basal Metabolic Rate in Series of Four Hundred and Ninety-Three Cases**

Basal Metabolism Rate	16 to 19 Years	20 to 29 Years	30 to 39 Years	40 to 49 Years	50 to 59 Years	60 to 69 Years
+ 15 to + 19.....	.....	1 case 0.8%	1 case 0.7%	3 cases 2.3%	.....	.....
+ 20 to + 29.....	3 cases 12.5%	8 cases 6.1%	7 cases 4.9%	9 cases 6.9%	3 cases 5.4%	1 case 11.1%
+ 30 to + 39.....	1 case 4.2%	17 cases 13.0%	21 cases 14.7%	14 cases 10.8%	12 cases 21.4%	2 cases 22.2%
+ 40 to + 49.....	4 cases 16.6%	19 cases 14.5%	24 cases 16.7%	17 cases 13.1%	7 cases 12.5%	1 case 11.1%
+ 50 to + 59.....	1 case 4.2%	23 cases 17.5%	24 cases 16.7%	28 cases 21.5%	9 cases 16%	.....
+ 60 to + 69.....	7 cases 29.1%	18 cases 13.7%	17 cases 11.9%	19 cases 14.6%	9 cases 16%	4 cases 44.4%
+ 70 to + 79.....	6 cases 25.0%	20 cases 15.3%	24 cases 16.7%	15 cases 11.5%	7 cases 12.5%	.....
+ 80 to + 89.....	1 case 4.2%	11 cases 8.4%	11 cases 7.7%	13 cases 10.0%	5 cases 8.9%	.....
+ 90 to + 99.....	.....	11 cases 8.4%	6 cases 4.2%	6 cases 4.6%	2 cases 3.6%	.....
+100 to +125.....	1 case 4.2%	3 cases 2.3%	8 cases 5.6%	6 cases 4.6%	2 cases 3.6%	1 case 11.1%
Number of cases...	24	131	143	130	56	9

* The sex incidence, in this group, is 12.5 per cent. male and 87.5 per cent. female.

pole ligation, skin flap elevation and subtotal thyroidectomy; skin flap elevation and two hemithyroidectomies; two double (inferior and superior) pole ligations and a subtotal thyroidectomy, and one double, one single pole ligation and a subtotal thyroidectomy.

Four-Stage.—Two single ligations and two hemithyroidectomies; one ligation, a skin flap elevation, two hemithyroidectomies; one double ligation, two single ligations, and a subtotal thyroidectomy, and three single ligations and a subtotal thyroidectomy.

Five Stage.—Four single ligations and a subtotal thyroidectomy; two ligations, a skin flap elevation and two hemithyroidectomies.

Six-Stage.—Four single ligations and two hemithyroidectomies.

Eight-Stage.—Seven hot water injections and a subtotal thyroidectomy (practiced in one case).

Of our series of primary hyperthyroidism cases, 38 per cent. had a one-stage operation; 62 per cent. had multiple stage operations; 35 per

cent. had a two-stage operation; 20 per cent. had a three-stage operation; 6 per cent. had a four-stage operation, and 1 per cent. had a five-stage, six-stage and eight-stage operation.

Of the 62 per cent. of cases which had multiple stage procedures, 11 per cent. had two hemithyroidectomies without ligation, and only 0.3 per cent. had skin flap elevations and operations on the gland without pole ligation; the rest, about 51 per cent. of the entire group, had ligation of the superior or inferior poles, single or double.

Table 3 shows the relationship of the number of stages of operative procedure to the height of the basal metabolic rate.

TABLE 3.—*Relationship of Number of Stages of Operative Procedure to Height of Basal Metabolic Rate*

Basal Metabolism Rate	No. of Cases	One-Stage	Two-Stage	Three-Stage	Four-Stage	Five-Stage	Six-Stage	Eight-Stage
+ 15 to + 19	7	(5) 71%	(2) 29%	.....	.....	.....	.....	.....
+ 20 to + 29	32	(25) 78%	(6) 19%	(1) 3%	.....	.....	.....	.....
+ 30 to + 39	67	(44) 66%	(17) 25%	(5) 7.5%	(1) 1.5%	.....	.....	.....
+ 40 to + 49	75	(47) 63%	(16) 21%	(12) 16%	.....	.....	.....	.....
+ 50 to + 59	97	(35) 36.5%	(43) 44.5%	(15) 15%	(2) 2.5%	(1) 1%	.....	.....
+ 60 to + 69	82	(22) 27.1%	(34) 41%	(17) 20.5%	(7) 8.5%	(2) 3%	.....	.....
+ 70 to + 79	64	(8) 12.5%	(33) 52%	(19) 29.5%	(4) 6%	.....	.....	.....
+ 80 to + 89	37	(6) 16%	(12) 32.5%	(12) 32.5%	(7) 19%	.....	.....	.....
+ 90 to + 99	27	(2) 7%	(8) 30%	(14) 52%	(3) 11%	.....	.....	.....
+100 to +120	20	(0) 0%	(5) 25%	(7) 35%	(5) 25%	(1) 5%	(1) 5%	(1) 5%
Totals.....	508	194	176	102	29	4	1	1

Table 3 shows that, in the cases with a basal rate of from + 15 to + 29, about 76 per cent. of the patients are operated on in one stage, whereas, in the two groups with a rate of from + 90 to + 120, only about 2 per cent. were considered operable in one stage. The two-stage procedure was done most frequently in the group with rates of from + 70 to + 79; the three-stage in the group with rates of from + 90 to + 99; the four-stage in the group with rates of from + 100 to + 120; while operations of five stages were performed in the groups with rates of from + 50 to + 59, + 70 to + 79, and + 100 to + 120. An operative procedure of six stages, all poles separately ligated and two subtotal hemithyroidectomies, was successfully done in a case of the group with the highest metabolic rate. One case, in the latter group, had eight stages (seven hot water injections at the time when this procedure was used in the clinic).

From these statistics, it seems fair to conclude that the metabolic rate, while not an absolutely accurate index for decision as to number of stages in operative procedure, is a moderately reliable guide.

Clinically, the effect of pole ligation is always beneficial. Patients, without exception, show a decrease in the pulse rate and nervous symptoms, an increased immunity to operative reaction, and, almost without exception, an increase in weight from 2 or 3 to 20 pounds (0.9 or

1.4 to 9 kg.). The effect on the metabolic rate is, however, by no means as constant. Table 4 was compiled in order to show the relationship of the preoperative level of the basal metabolic rate to the effect of pole ligation. Beginning with the group of cases showing a preoperative level of the basal metabolic rate of from + 30 to + 39, the ligated cases are grouped and the effect of single or multiple pole ligation on the metabolic rate is demonstrated. The rates used are those obtained on the day preceding ligation and again six weeks after ligation, immediately preceding operation on the gland. The six weeks intervening between ligation and operation on the gland are spent as much as possible in rest, so that this factor as well as the ligation procedure contributes to the effect on the metabolic rate.

A study of Table 4 shows that whereas, in the group of + 30 to + 39, only 35 per cent. of the cases showed metabolic evidence of improvement as indicated by a drop in the rate, the percentage of cases showing a drop after ligation progressively increases with the preoperative height. In the + 90 to + 99 class, 87.5 per cent. and, in the + 100 to + 120 class, 100 per cent. show a lower rate six weeks after ligation. It has always been a cause for surprise to find that certain cases, although clinically improved after pole ligation, show an increased metabolic rate. Table 4 shows that this anomaly is of much more frequent occurrence in the lower metabolic groups and progressively diminishes as the rate ascends. Judged from the metabolic standpoint alone, therefore, pole ligation would seem to be more generally purposeful when the original metabolic rate is above + 50.

Sixty cases in which the operative procedure consisted of two subtotal hemithyroidectomy operations without previous pole ligation were studied with reference to the effect on the metabolic rate of the first right-sided operation. Table 5 shows the results in these cases:

The series is not a large one as many of the hemithyroidectomy operations were done following pole ligation, and in other cases the second hemithyroidectomy was done five or six days after the first with no intervening test of the basal metabolic rate. In this small series, however, only seven of the sixty cases (12 per cent.) show an increased rate after one-stage hemithyroidectomy, and these are in the groups below + 69; 8 per cent. remained at the same level, and 80 per cent. showed a drop in the rate. In the group above + 59, the drop is almost constant, while below this level, three of the groups show a rather high percentage of rise in rate, though the series is too small in these groups to be of much value for comparison.

In the whole series as compared with the 200 cases in which pole ligation was done, the procedure is definitely though not considerably more effective from the point of view of basal metabolic rate than the ligation procedure.

TABLE 4.—*Effect on Basal Metabolic Rate of Pole Ligation Procedures in Two Hundred Cases*

Groups of cases, classified according to height of basal metabolic rate

Level of Basal Metabolic Rate (Before Ligation)	Rate Dropped	Rate Remained at Same Level	Rate Rose
+30 to +39.....	To the +15 to +19 level, 1 case	.....	To the +40 to +49 level, 6 cases
14 cases (20% of the group of 70 cases showing this preoperative rate)	To the +20 to +29 level, 4 cases	1 case	To the +50 to +59 level, 1 case To the +60 to +69 level, 1 case
	5 cases 35%	1 case 7%	8 cases 58%
+40 to +49.....	To the +15 to +19 level, 1 case	.....	To the +50 to +59 level, 6 cases
21 cases (28% of the group of 75 cases showing this preoperative rate)	To the +20 to +29 level, 3 cases To the +30 to +39 level, 3 cases	6 cases	To the +60 to +69 level, 1 case To the +70 to +79 level, 1 case
	7 cases 33%	6 cases 29%	8 cases 38%
+50 to +59.....	To the +15 to +19 level, 1 case	.....	To the +60 to +69 level, 5 cases
28 cases (30% of the group of 92 cases showing this preoperative rate)	To the +20 to +29 level, 3 cases To the +30 to +39 level, 4 cases To the +40 to +49 level, 7 cases	..... 5 cases	To the +70 to +79 level, 2 cases To the +80 to +89 level, 0 cases To the +90 to +99 level, 1 case
	15 cases 54%	5 cases 18%	8 cases 28%
+60 to +69.....	To the +15 to +19 level, 0 cases	.....	To the +70 to +79 level, 2 cases
37 cases (41% of the group of 90 cases showing this preoperative rate)	To the +20 to +29 level, 3 cases To the +30 to +39 level, 1 case To the +40 to +49 level, 7 cases To the +50 to +59 level, 13 cases	.... 9 cases	To the +80 to +89 level, 2 cases To the +90 to +99 level, 0 cases
	24 cases 65%	9 cases 24%	4 cases 11%
+70 to +79.....	To the +15 to +19 level, 0 cases	.....	To the +80 to +89 level, 4 cases
40 cases (57% of the group of 70 cases showing this preoperative rate)	To the +20 to +29 level, 3 cases To the +30 to +39 level, 2 cases To the +40 to +49 level, 2 cases To the +50 to +59 level, 12 cases To the +60 to +69 level, 12 cases	.... 4 cases	To the +90 to +99 level, 0 cases To the +100 level, 1 case
	31 cases 77.5%	4 cases 10%	5 cases 12.5%
+80 to +89.....	To the +15 to +19 level, 0 cases	.....	To the +90 to +99 level, 2 cases
28 cases (70% of the group of 40 cases showing this preoperative rate)	To the +20 to +29 level, 2 cases To the +30 to +39 level, 1 case To the +40 to +49 level, 5 cases To the +50 to +59 level, 3 cases To the +60 to +69 level, 2 cases To the +70 to +79 level, 9 cases	.... 3 cases	To the +100 level, 1 case
	22 cases 78%	3 cases 11%	3 cases 11%
+90 to +99.....	To the +15 to +19 level, 0 cases	.....	To the +100 level, 1 case
16 cases (57% of the group of 28 cases showing this preoperative rate)	To the +20 to +29 level, 0 cases To the +30 to +39 level, 1 case To the +40 to +49 level, 0 cases To the +50 to +59 level, 3 cases To the +60 to +69 level, 8 cases To the +70 to +79 level, 1 case To the +80 to +89 level, 1 case	.... 1 case	
	14 cases 87.5%	1 case 6.25%	1 case 6.25%
+100 to +120.....	To the +15 to +19 level, 0 cases		
16 cases (80% of the group of 20 cases showing this preoperative rate)	To the +20 to +29 level, 0 cases To the +30 to +39 level, 0 cases To the +40 to +49 level, 0 cases To the +50 to +59 level, 2 cases To the +60 to +69 level, 3 cases To the +70 to +79 level, 4 cases To the +80 to +89 level, 1 case To the +90 to +99 level, 6 cases	0 cases	0 cases
	16 cases 100%	0 cases 0%	0 cases 0%
200 cases	134 cases 67%	29 cases 14.5%	37 cases 18.5%

It is our practice to estimate the basal matabolic rate on the sixth day after operation, and again every two months for six months, and, finally, again at the end of a year. By this method of following up the cases, we detect persistent or recurring hyperthyroidism, as in our

TABLE 5.—*Effect on Basal Metabolic Rate of One Subtotal Hemithyroidectomy as a First Stage Operative Procedure in Sixty Cases*

Level of Basal Metabolic Rate (Before Hemithyroidectomy)	Rate Dropped	Rate Remained at Same Level	Rate Rose
+15 to +19..... 1 case	To the +6 to +15 level, 1 case 1 case 100%	0 cases	0 cases
+20 to +29..... 2 cases	..... 0 cases	0 cases	To the +40 to +49 level, 2 cases 2 cases 100%
+30 to +39..... 8 cases	To the +5 to +15 level, 1 case To the +15 to +19 level, 1 case To the +20 to +29 level, 1 case 3 cases 37.5%	4 cases 50%	To the +40 to +49 level, 1 case 1 case 12.5%
+40 to +49..... 6 cases	To the +20 to +29 level, 3 cases To the +30 to +39 level, 3 cases 6 cases 100%	0 cases	0 cases
+50 to +59..... 13 cases	To the +30 to +39 level, 3 cases To the +40 to +49 level, 6 cases 9 cases 69%	1 case 8%	To the +60 to +69 level, 2 cases To the +80 to +89 level, 1 case 3 cases 23%
+60 to +69..... 15 cases	To the +20 to +29 level, 2 cases To the +30 to +39 level, 4 cases To the +40 to +49 level, 4 cases To the +50 to +59 level, 4 cases 14 cases 93%	0 cases 0 cases	To the +80 to +89 level, 1 case 1 case 7%
+70 to +79..... 10 cases	To the +20 to +29 level, 2 cases To the +30 to +39 level, 3 cases To the +40 to +49 level, 4 cases To the +50 to +59 level, 1 case To the +60 to +69 level, 0 cases 10 cases 100%	0 cases	0 cases
+80 to +89..... 2 cases	To the +15 to +19 level, 1 case To the +50 to +59 level, 1 case 2 cases 100%	0 cases	0 cases
+90 to +99..... 3 cases	To the +40 to +49 level, 1 case To the +50 to +59 level, 1 case To the +60 to +69 level, 1 case 3 cases 100%	0 cases	0 cases
60 cases	48 cases 80%	5 cases 8%	7 cases 12%

opinion, unless a patient's basal rate drops to within normal limits and remains there, he has not been cured of his hyperthyroidism. In these primary hyperthyroidism cases, 37.4 per cent. dropped to a point below + 20 in six days after completion of the operative procedure.

Table 6 shows the percentage of cases within each group which return to approximately the normal rate in six days after the completed operation.

The group in Table 6 in which the largest percentage of cases (58 per cent.) showed a drop to below + 20 in six days after operation is the + 30 to + 39 group, and with an increase in rate there is a gradual decrease in the percentage of cases showing this immediate metabolic evidence of cure, except in the group of + 90 to + 99, in which there is a slightly higher percentage than in the + 70 to + 79 group.

TABLE 6.—*Percentage of Cases Within Each Group Which Have Basal Metabolism Rate Below + 20 in Six Days After Operation*

Groups	
+20 to +29	44% of 32 cases
+30 to +39	58% of 70 cases
+40 to +49	49% of 75 cases
+50 to +59	41% of 92 cases
+60 to +69	32% of 90 cases
+70 to +79	20% of 70 cases
+80 to +89	10% of 40 cases
+90 to +99	28% of 28 cases
+100	0% of 20 cases

Total percentage of cases showing immediate drop (six days after operation), 37.4%

The cases that show a more gradual drop to normal rate, 55.9 per cent. of the entire group, usually show in the three tests which follow the operation at two-month intervals a decrease to within normal limits within from two to six months. We expect that they will have a rate below + 15 at the end of six months. If this does not occur, we believe that the surgical treatment has been inadequate, and that the patient is suffering from persistent hyperthyroidism. Many of the cases which come to us from other clinics as recurrent cases we consider may well be cases of persistent hyperthyroidism in which the treatment, surgical or roentgenologic, has been inadequate. Of our own cases in this series, thirty-six cases, or 6.7 per cent., have failed to show a normal rate after six months. Such cases, without exception, showed some clinical signs of persistent hyperthyroidism even though the larger part of the burden of the disease had been removed. All such patients are considered only partially relieved, and are advised to have further surgical treatment.

Table 7 shows the preoperative rates and the type of operation in these thirty-six cases.

From Table 7, it may be seen that the highest percentages of cases showing inadequate results from operative treatment have preoperative metabolic rates between + 50 and + 79, twenty-two out of the thirty-six cases, or 61 per cent., being in these groups. In fact, 8.7 per cent. of the patients in these three groups of cases fail to reach a normal metabolic rate in six months.

In the primary hyperthyroidism group, thirteen out of the 533 patients, or 2.4 per cent., have been readmitted to the clinic and reoperated on for persistent or recurring hyperthyroidism. The first preoperative rates in these thirteen cases were in the following groups: From + 30 to + 39, one case; + 40 to + 49, two cases; + 50 to + 59, one case; + 60 to + 69, three cases; + 70 to + 79, two cases; + 80 to + 89, none; + 90 to + 99, one case, and + 100 to + 120, three cases.

Only two of these patients showed, between the first and second operation, a drop to normal rate and later a rise in rate, indicating a recurrence of the disease. Eleven patients, or 85 per cent., failed to show an adequate fall in the metabolic rate, and continued to have

TABLE 7.—*Analysis of Thirty-Six Cases That Failed to Show a Normal Rate Six Months After Operation*

	Type of Operation				
Preoperative Rate	(1) Subtotal Thyroidectomy Without Preliminary Operation	(2) Two Hemithyroidectomies Without Preliminary Ligation	(3) Operation on Gland (Subtotal Thyroidectomy or Hemithyroidectomies) with Preliminary Ligations	Totals	Percentage of Metabolic Group
+ 20 to + 29.....	1 case	.....	.....	1 case	3%
+ 30 to + 39.....	1 case	.....	.....	1 case	1.5%
+ 40 to + 49.....	.....	.....	3 cases	3 cases	4%
+ 50 to + 59.....	3 cases	1 case	3 cases	7 cases	9%
+ 60 to + 69.....	1 case	4 cases	3 cases	8 cases	8.5%
+ 70 to + 79.....	.....	1 case	6 cases	7 cases	10%
+ 80 to + 89.....	1 case	.....	1 case	2 cases	3%
+ 90 to + 99.....	.....	.....	3 cases	3 cases	1%
+100 to +120.....	1 case	.....	3 cases	4 cases	2%
Totals.....	8 cases*	6 cases	22 cases	36 cases	

* It is interesting to note that three of these eight cases came to our clinic from other clinics where subtotal thyroidectomies had been performed and had failed to cure. In these cases, Lugol's solution proved valuable, as will be discussed in a later paper.

symptoms at a period from six months to three years after the first operation. Eight of these eleven cases were relieved immediately by the second operation, and showed an immediate drop to normal in the basal metabolic rate. Three, however, persisted in showing a rate slightly above normal (in the + 20 to + 29 group) even after the second operation, though the patients were greatly improved clinically.

The complication of diabetes mellitus is occasionally seen in our cases of hyperthyroidism. All patients showing persistent glycosuria are referred to Dr. Joslin's staff for examination, and those proved diabetic are prepared for operation with insulin and diabetic precautions. A large number of our cases have slight and transient glycosuria on admission, with urine sugar from 0.1 to 1.5 per cent. Fourteen of our 533 cases of primary hyperthyroidism were definitely diabetic. These fourteen cases (2.6 per cent. of the series) showed preoperative basal

metabolic rates in the following groups: From + 20 to + 29, one case; + 30 to + 39, one case; + 40 to + 49, one case; + 50 to + 59, six cases; + 60 to + 69, two cases; + 70 to + 79, one case, and + 80 to + 89, two cases.

Five of the fourteen cases (35 per cent.) had single stage operations, two (15 per cent.) had two hemithyroidectomies, and the other seven (50 per cent.) had preliminary pole ligation. Although this group is very small for comparison with the entire primary hyperthyroidism group, it is seen that these percentages coincide almost exactly with those of the whole group, from which it is suggested that the diabetes complication did not increase the indication for multiple stage procedure. The ages of these diabetic patients, on admission, ranged from 14 to 57 years. The relationship of preoperative basal metabolic rate to age is shown in Table 8.

Four of the fourteen cases failed to reach a normal metabolic rate in six months after operation, although pulse rate and other clinical signs gave evidence of improvement. This is by comparison with these data in the larger group a high percentage (28 per cent.), and if it con-

TABLE 8.—*Relationship of Preoperative Basal Metabolic Rate to Age*

	+20 to +29	+30 to +39	+40 to +49	+50 to +59	+60 to +69	+70 to +79	+80 to +89
10 to 20 years	.....	.....	.....	.....	1 case	.....	.....
20 to 30 years	.....	.....	.....	2 cases	.....	.....	.....
30 to 40 years	1 case	.....	.....	1 case	.....	1 case	1 case
40 to 50 years	.....	1 case	1 case	1 case	1 case	.....	1 case
50 to 60 years	.....	.....	.....	2 cases	.....	.....	.....

tinues to be true in a larger series might suggest the possibility of an interrelationship of function between pancreas and thyroid, which is still obscure. Another rather suggestive fact is the occurrence, in the past history of two of these diabetic hyperthyroid patients, first of definite attacks of hyperthyroidism—in one case treated surgically, and in the other untreated—followed in one or two years by diabetes and, later, by recurrences of hyperthyroidism. A third patient, a woman, aged 26, had a preoperative rate of + 51 and no glycosuria during her surgical treatment for hyperthyroidism. Her basal metabolic rate reached normal limits in four months after the completion of the operative treatment, and she was apparently well. Two years later, however, she was readmitted to the hospital for diabetes, and showed a metabolic rate of + 24 with corresponding clinical evidence of hyperthyroidism.

The cardiac complications of hyperthyroidism and their relation to the basal metabolic rate have already been discussed by Hamilton,[2] and will therefore be omitted from this paper.

2. Hamilton, B. E.: Heart Failure of Congestive Type Caused by Hyperthyroidism, J. A. M. A. **83**:405 (Aug. 9) 1924.

Eighteen cases of this primary hyperthyroidism series (3.3 per cent.) had postoperative rates below normal limits [3] (between — 16 and — 27) and from the metabolic point of view alone would have been classed as operative myxedema. Five only (0.9 per cent.), however, showed clinical signs of myxedema, requiring treatment with thyroxin. The preoperative rates, in these cases, ranged from the + 30 group to the + 80 group. The thirteen cases showing rates below — 15 but without symptoms have all, later, had higher rates without treatment, suggesting a readjustment of function of the gland.

Of this group of primary hyperthyroidism cases, nine patients (1.7 per cent.) died within two days of operation, in one case following single ligation of a superior pole; in the other cases following more extensive operations on the gland. Three other patients died at home following a first stage procedure, one apparently of cerebral hemorrhage, another of an acute exacerbation of the disease after a severe emotional shock.

The 320 cases of tumors with secondary hyperthyroidism were of the following types: Single adenoma, 119, or 37.1 per cent.; multiple

TABLE 9.—*Percentage of Incidence in Three Hundred and Thirteen Cases, Grouped According to Preoperative Basal Metabolic Rate*

Rate	Number of Cases	Per Cent.
+ 15 to + 19	41	13.1
+ 20 to + 29	82	26.2
+ 30 to + 39	75	24.0
+ 40 to + 49	38	12.1
+ 50 to + 59	29	9.2
+ 60 to + 69	19	6.1
+ 70 to + 79	17	5.4
+ 80 to + 89	5	1.6
+ 90 to + 99	2	0.6
+100 to +125	5	1.6

adenomas, 27, or 8.4 per cent.; multiple colloid adenomas, 145, or 45.2 per cent.; colloid goiters, 22, or 7 per cent.; adenoma with coincident hyperplasia of thyroid, 1, or 0.3 per cent., and cysts, 6, or 2 per cent.

Thirty-one cases of the adenomatous type were partly intrathoracic and six were completely intrathoracic without evidence of goiter in the neck.

The percentage of incidence of this group [4] of cases, grouped according to the preoperative rate of basal metabolism, is given in Table 9.

The percentage of incidence in the different groups shows a striking contrast to that in the primary hyperthyroidism series, in which the high incidence occurred in the + 50 to + 69 groups, while in these

3. In our experience, the low limit of normal may be placed at — 15.

4. Seven of these 320 cases did not have satisfactory preoperative tests of the basal metabolic rate and are therefore not included in the series.

cases of secondary hyperthyroidism more than than 75 per cent. have a preoperative basal metabolic rate of less than + 50.

The ages of the patients in the secondary hyperthyroidism group, when first seen in the clinic (usually a few months after the onset of symptoms of hyperthyroidism and from several months to many years after the first appearance of the goiter), ranged from 15 to 79 years. Table 10 shows the relationship of age to preoperative basal metabolic rate in a series of 322 cases.

The secondary hyperthyroidism patients were operated on, in large part (92.2 per cent.), in one stage. This one-stage procedure consists of: Excision of the adenoma or cyst; enucleation of the adenoma with reconstruction of the lobes; subtotal hemithyroidectomy, and subtotal thyroidectomy.

TABLE 10.—*Relationship of Age to Preoperative Basal Metabolic Rate in Three Hundred and Twenty-Two Cases*

Basal Metabolism Rate	15 to 19 Years	20 to 29 Years	30 to 39 Years	40 to 49 Years	50 to 59 Years	60 to 69 Years	70 to 79 Years
+ 15 to + 19.....	1 case 11.1%	7 cases 15.2%	9 cases 13.0%	11 cases 12.5%	7 cases 11.5%	6 cases 13.96%	.....
+ 20 to + 29.....	1 case 11.1%	14 cases 30.4%	21 cases 30.0%	29 cases 32.96%	10 cases 16.5%	9 cases 20.96%	2 cases 33.3%
+ 30 to + 39.....	2 cases 22.2%	10 cases 21.7%	12 cases 17.4%	22 cases 25.0%	21 cases 34.5%	8 cases 18.6%	1 case 16.7%
+ 40 to + 49.....	3 cases 33.3%	4 cases 8.7%	11 cases 16.0%	6 cases 6.8%	6 cases 9.6%	6 cases 13.96%	2 cases 33.3%
+ 50 to + 59.....	1 case 11.1%	4 cases 8.7%	6 cases 8.7%	8 cases 9.1%	5 cases 8.2%	8 cases 18.6%	.....
+ 60 to + 69.....	.....	.....	4 cases 5.8%	3 cases 3.5%	7 cases 11.5%	2 cases 4.65%	1 case 16.7%
+ 70 to + 79.....	1 case 11.1%	3 cases 6.5%	3 cases 4.35%	5 cases 5.65%	4 cases 6.55%	2 cases 4.65%	.....
+ 80 to + 89.....	.....	3 cases 6.5%	1 case 1.45%	1 case 1.1%	1 case 1.65%	.....	.....
+ 90 to + 99.....	.....	.....	.....	.....	.....	2 cases 4.65%	.....
+100 to +125.....	.....	1 case 2.2%	2 cases 2.9%	3 cases 3.4%	.....	.....	.....
Number of cases*.....	9	46	69	88	61	43	6

* The sex incidence is 8.7 per cent. male and 91.3 per cent. female.

Twenty-five cases (7.8 per cent.) had multiple stage procedure, which consisted of ligation of the poles with subsequent subtotal thyroidectomy or hemithyroidectomies in fifteen cases (4.7 per cent.[5]), and two subtotal hemithyroidectomies in ten cases (3.1 per cent.).

The relation of the number of stages in the multiple stage operative procedure to the preoperative rate of basal metabolism in these twenty-five cases is given in Table 11.

5. Two patients with preoperative rates of + 123 and + 125 had five-stage and six-stage operations, ligation of both superior poles (and in one case also of one inferior pole), elevation of the skin flap and two subtotal hemithyroidectomies.

The two-stage procedure was used in the two cases of the + 20 to + 29 group; in one case there was cardiac decompensation, and in the other the patient, a woman, was 70.

Six patients of this group (1.9 per cent.) failed to have a normal rate after six months, although clinically well. One of these six patients reached a normal limit after one year. Three patients (0.9 per cent.) had recurrences of the adenomas, one without hyperthyroidism, two with hyperthyroidism.

Three patients (0.9 per cent.) had postoperative rates below — 20, one without clinical evidence of myxedema, the other two with definite signs of myxedema requiring thyroxin up to the present.

Five patients (1.5 per cent.) had diabetes mellitus as a complicating factor. Three of these patients had a normal convalescence, while two died.

TABLE 11.—*Relation of Number of Stages in Multiple Stage Operation to Preoperative Rate in Twenty-Five Cases*

Preoperative Basal Metabolic Rate	Cases		Number of Cases				
			Two-Stage	Three-Stage	Four-Stage	Five-Stage	Six-Stage
+ 15 to + 19	0 out of 41	(0%)	...	...	...	...	...
+ 20 to + 29	2 out of 82	(2.4%)	2	...	...	...	...
+ 30 to + 39	1 out of 75	(1.3%)	1	...	...	...	...
+ 40 to + 49	2 out of 38	(5.2%)	2	...	...	...	...
+ 50 to + 59	1 out of 29	(3.4%)	1	...	...	...	...
+ 60 to + 69	7 out of 19	(36%)	4	3	...	...	...
+ 70 to + 79	5 out of 17	(29%)	4	...	1	...	...
+ 80 to + 89	2 out of 5	(40%)	2	...	...	...	...
+ 90 to + 99	0 out of 2	(0%)	...	...	...	...	...
+100 to +125	5 out of 5	(100%)	...	1	2	1	1
	25 out of 313	(7.8%)	16	4	3	1	1

The deaths, in this series, numbered seven (2.1 per cent.), a higher mortality than in the group of primary hyperthyroidism cases.

Comparison of the statistical data of primary and of secondary hyperthyroidism reveals the following facts:

1. The preoperative basal metabolic rate in primary hyperthyroidism was, in 64.6 per cent. of the cases, above + 50, and, in 35.4 per cent. of the cases, below + 50. The preoperative basal metabolic rate in secondary hyperthyroidism was, in 24.5 per cent. of the cases, above + 50, and, in 75.4 per cent. of the cases, below + 50.

2. The multiple stage operation was practiced in primary hyperthyroidism in 62 per cent. of the cases. In secondary hyperthyroidism, only 7.8 per cent. had a multiple stage operation.

3. The relation of the number of stages to the preoperative height of basal metabolic rate is much more definite in primary hyperthyroidism than in secondary hyperthyroidism.

4. In the primary hyperthyroidism series, 6.7 per cent. failed to show a normal rate after six months. In the secondary hyperthyroidism group, only 1.9 per cent. failed to reach normal in six months.

5. Reoperation for recurrences or for persistence of hyperthyroidism occurred in 2.4 per cent. of the primary hyperthyroidism cases, and in only 0.9 per cent. of the secondary hyperthyroidism cases.

6. Diabetes mellitus occurred in 2.6 per cent. of the primary hyperthyroidism group, and in 1.5 per cent. of the secondary hyperthyroidism group.

7. Postoperative myxedema occurred in 0.9 per cent. of the primary hyperthyroidism cases, and in 0.9 per cent. of the secondary hyperthyroidism.

8. The mortality in primary hyperthyroidism was 1.7 per cent., and in secondary hyperthyroidism was 2.1 per cent.

TABLE 12.—*Analysis of Three Hundred and Ninety Benign Tumors Without Hyperthyroidism*

	Cases	Per Cent.
Single adenomas (right lobe, 54.3%; left lobe, 35%; isthmus, 10.7%)	201	51.5
Multiple adenomas	32	8.2
Multiple colloid adenomas	112	28.7
Colloid goiters	26	6.7
Cysts	13	3.3
Thyroglossal cysts*	1	0.3
Thyroiditis	4	1
Lingual thyroid	1	0.3

* Usually the thyroglossal cyst cases are not referred to the metabolism laboratory, and are therefore not included in this series of cases. The case included here was doubtfully diagnosed, and therefore had a preoperative basal metabolic test.

The 390 patients operated on for benign tumors without hyperthyroidism had tumors of the types given in Table 12.

Forty-five of the 390 cases were partly intrathoracic, and five completely within the thorax with no evidence of goiter in the neck. Six surrounded the trachea and esophagus, causing severe dyspnea and dysphagia. The preoperative rates, in these cases, were between — 10 and + 15.

The operative procedure was similar to that in the cases of secondary hyperthyroidism and consisted of: Enucleation of the adenomas or cysts, with or without reconstruction of the lobes; subtotal hemithyroidectomy; subtotal thyroidectomy, and excision of a specimen of thyroid tissue for differential diagnosis (thyroiditis or malignancy).

Only one case had a multiple stage procedure—this consisting of elevation of the skin flap with a subtotal thyroidectomy three days later.

The postoperative rates, in these cases, remained within normal limits, except in those cases in which operative myxedema followed removal of an obstructive goiter. Such cases numbered 7, or 1.8 per cent., and these required treatment with thyroxin. A few cases of this

group, as in the secondary hyperthyroidism group, showed an immediate drop to a rate below — 15 but without clinical evidence of myxedema. The rate of these patients invariably rose later without treatment to a normal metabolic rate.

An interesting group, in this series, is that of seven cases that showed preoperatively a rate below — 10 (from — 11 to — 31) and, after enucleation of adenomas with reconstruction of the lobes, had rates from — 10 to + 13. In such cases, we feel that normal thyroid tissue was compressed by the adenomas and that normal thyroid function followed relief of this pressure by removal of the adenomas.

Four of these cases were recurrent adenomas or multiple colloid adenomas previously operated on at other clinics. Up to the present, there have been no recurrences among the patients of this group operated on in our clinic.

Only one case in this group (a single adenoma) had diabetes mellitus as a complicating factor, which, however, had no apparent effect on the treatment of the thyroid condition.

The deaths in this group numbered two (0.51 per cent.), and were due in both cases to mediastinitis. In one case in which the patient had a recurrent multiple colloid adenomatous goiter with a preoperative rate of — 11, death occurred on the twenty-fourth day after operation. In the other case, with a preoperative rate of + 11, the patient died five days after operation.

The fifteen cases of malignancy of the thyroid consisted of fourteen carcinomas and one sarcoma. All but three had preoperative rates below + 15. Of these three, one had a preoperative rate of + 26 with no subsequent test. One had a preoperative rate of + 32 with a drop to + 1 after a left hemithyroidectomy; in this case, the left lobe only was involved. The third was diagnosed preoperatively as a multiple colloid adenomatous goiter with secondary hyperthyroidism, his preoperative rate being + 72. Two subtotal hemithyroidectomies were done, and the rate dropped to — 6. Tissue from the left lobe showed carcinoma, and the patient, a boy, aged 18, is now being treated with roentgen ray. Four of the fifteen cases were not preoperatively suspected of malignancy, which was determined only by pathologic examination of the tissue removed.

The patients of this series who were not operated on, 417 in number, were referred to the metabolism laboratory for diagnosis, and were found to have no thyroid disease in 400 cases, and in seventeen cases to have myxedema. The latter group had rates, before beginning treatment, from — 16 to — 44, and were invariably brought to normal by the use of thyroid extract or thyroxin. In most cases, better clinical results were produced by large doses of thyroxin or thyroid extract in the beginning, which brought the rate rapidly up to from + 15 to + 25,

with a subsequent decrease in the dosage sufficient to hold the rate at a point between — 5 and + 15. It is, in our opinion, impossible to begin or to continue treatment of myxedema without frequent estimations of the basal metabolic rate.

Of the 400 patients who were found, by tests of the metabolic rate, to have no thyroid disease, a large number had clinical symptoms and signs closely simulating hyperthyroidism. It is frequently impossible even for the clinician who is thoroughly familiar with hyperthyroidism to differentiate between this condition and the neurocirculatory asthenia or effort syndrome which may resemble it in every respect except one, namely, that hyperthyroidism is inevitably accompanied by an elevation in the metabolic rate while neurocirculatory asthenia shows normal basal metabolic rates. The picture is especially complicated if the neurocirculatory asthenic has a coincident simple goiter, adenoma-like, colloid or adolescent. A further complication is the fact that neurocirculatory asthenic patients, almost without exception, have an elevated rate during the first test of their basal metabolism. This rate is usually between

TABLE 13.—*Rate of Basal Metabolism in Woman, Aged 27, with Diagnosis of Neurocirculatory Asthenia*

Date	Metabolic Rate	Pulse Rate	Body Weight	
			Pounds	Kg.
3/2/23	+23	86-110	99	(44.9)
3/3/23	+16	94-110	100.3	(45.5)
3/4/23	+10	92-108	100.3	(45.5)

+ 16 and + 30, and with subsequent tests on subsequent days and the gradual adaptation of the nervous person to the technic of the test, this rate descends invariably to one below + 15. The typical course of this descent is shown in Table 13.

When the elevated basal metabolic rate is due to true active hyperthyroidism, however, it always remains definitely above the normal limit, even though it may show a drop of 10 to 20 points from a high rate while the patient rests several days in bed. For example, the condition of a young woman invalided for three years was diagnosed differently by various members of the clinic; some felt that she was a neurocirculatory asthenic patient, and others were of the opinion that she was definitely a hyperthyroidism patient. Her basal metabolic rate remained above + 30 in five tests. A subtotal thyroidectomy was done with an immediate drop in the rate to + 11. Three months later, her rate was — 1; her symptoms were completely relieved, and she was leading a normal life. The course of her basal metabolic rate during diagnosis and treatment is given in Table 14.

It is clear that accuracy in the technic and repetition of the tests, until one is convinced that the patient has become thoroughly adapted to

the test, are absolutely necessary in the differential diagnosis of these two conditions. It is not infrequently true that there is a fluctuation not only in the final results of the tests in the case of the neurocirculatory asthenic but also in the two-minute readings within the periods; this shows a lack of balance which is in keeping with their disorder. This fluctuation, like the elevation of rate, is gradually eliminated, however, by repetition of the tests.

In no part of the work of the clinic is the test of the basal metabolic rate of as much value as in the differential diagnosis of primary hyperthyroidism and neurocirculatory asthenia, for by it numerous patients, suspected of having hyperthyroidism, some of whom before the determination of the metabolic rate would probably have been operated on, are proved to have no thyroid disease.

TABLE 14.—*Rate of Basal Metabolism in Woman, Aged 29, with Primary Hyperthyroidism*

Date	Metabolic Rate	Pulse Rate	Body Weight		Operation
			Pounds	Kg.	
1/10/24.....	+44	108-148	103.5	(46.9)	
1/11/24.....	+42	130-134	103.5	(46.9)	
1/12/24.....	+36	104-118	102	(46.3)	
1/13/24.....	+38	112-128	102.5	(46.5)	
1/20/24.....	+33	112-128	103.5	(46.9)	
1/21/24.....	....	.....	.....	.....	Subtotal thyroidectomy
1/29/24.....	+11	104-116	100.5	(45.6)	
5/ 2/24.....	—1	84- 86	110.5	(50.1)	

CONCLUSIONS

1. The determination of the basal metabolic rate is of undoubted value in a clinic for thyroid disease: (*a*) to differentiate between hyperthyroidism and other conditions simulating this disease, especially neurocirculatory asthenia; (*b*) to differentiate between tumors of the thyroid with hyperthyroidism and those without it; (*c*) to aid in the estimation of the severity of the disease in both primary and secondary hyperthyroidism, thereby procuring definitely helpful data in the decision as to the extent of operative procedures throughout the treatment of the condition; (*d*) to estimate the adequacy of surgical treatment and the necessity for further treatment, when the usual procedure has been inadequate, and (*e*) to guide the treatment of myxedema.

2. The clinical results of surgical treatment in the group of 1,258 patients that had been operated on are consistently indicated by the changes in the metabolic rate.

APPENDECTOMY

A STUDY IN TECHNIC*

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The reaction of endothelial tissue to surgical trauma, by the more or less constant formation of abnormal adhesions, indicates that nearly all surgery within the peritoneal cavity is nothing more than an exchange of one abnormality for another. The ratio of this exchange determines directly the success of the operation. And too often, owing to this endothelial susceptibility, surgery within many peritoneal cavities results in nothing more than a traumatic truce.

That crippling of the parietal and omental adhesions follows the majority of operations for removing the appendix can be demonstrated at later operations during an exploration of the ileocecal segment. These adhesions, which appear rather conspicuous for the accorded simplicity of the operation, are often of little practical significance; but in a sufficient number of instances they are very undesirable. To them can often be attributed localized pain and tenderness, the onset of a previously absent sluggish cecum, and even operable and fatal intestinal obstructions. Another factor bearing on surgical technic is that of postoperative infections, from a mild wound contamination to a fatal peritonitis, which too frequently occur.

It is evident that the operation of appendectomy is in need of greater consideration than it has received. It should be looked on as more than the mere removal of the vermiform appendix, owing to the fact that the indirect results are at least as essential as the direct. The cecum, which bears the brunt of the operation, should be given primary consideration, in that it possesses rather distinctive characteristics, e. g., the highest bacterial content and the thinnest walls of any portion of the intestinal tract. Furthermore, it is a diverticulum and in order to carry on its most essential rôle in colonic peristalsis, it must have the utmost freedom of restricting adhesions, a most natural requirement of a functioning diverticulum.

The object of this paper is to discuss briefly: (1) an intraperitoneal observation of the ileocecal segment in 105 patients from whom the appendix had previously been removed; (2) two avoidable sources of adhesions, and (3) a series of 200 bacteriologic experiments that prove the frequency of two previously unrecognized, or unappreciated, sources of infection during the operation of removing the chronically diseased appendix.

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*The purulent appendix is not considered in this paper.

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ADHESIONS

In 105 explorations of the cecum, I found postappendectomy adhesions present in ninety-eight, and of these only eight were of negative significance, i. e., more or less of cobweb nature or solitary and nonobstructive. They will not be considered. Of the ninety remaining, the adhesions were of a type: (1) to cause an interference with the peristalsis of the cecum; (2) to cause localized pain and tenderness, and (3) to be looked on as a potential point of small bowel obstruction. The following description is offered based on the most dominating type of adhesions. In eight of the ninety patients, the cecum was adherent to the anterior parietal peritoneum in the line of the previous incision; in four of this group the adhesion was firm and the patients complained of localized pain and tenderness. In sixty of the ninety patients, the great omentum was adherent to the head of the cecum, covering the previous appendix site and the meso-appendix stump. In eleven of the ninety patients, loops of the terminal ileum were adherent to the meso-appendix stump and to the head of the cecum; the great omentum also was adherent to the meso-appendix stump and to the head of the cecum in five instances. In this group there occurred three small bowel obstructions, two due to bands from the old meso-appendix stump and one due to a band from the site of the previous appendix stump. In the remaining eleven of the ninety patients, the adhesions were so confusing as to defy description; loops of the terminal ileum, the great omentum and the cecum were so adherent, en masse, and even to the anterior abdominal wall, that the area primarily at fault was indiscernible. Thirty-two of the ninety patients complained of a constipation starting for the first time after the appendectomy. In every one of these operatively constipated patients, the cecum was adherent in a manner whereby its function as a contracting diverticulum was interfered with.

The significance of this study of 105 postappendectomy patients is: (1) In ninety (85 per cent.) crippling adhesions were found; (3) in thirty-two of these ninety patients (35 per cent.), a previously absent constipation occurred following the operation, and (3) in three of the ninety patients (more than 3 per cent.) intestinal obstruction occurred. This no doubt may be an unusually frequent occurrence; but it is very significant. Not to be disregarded are the four out of the eight whose cecums were adherent to the anterior abdominal wall and who complained of localized pain and tenderness beneath the scar.

The two most overlooked factors in the etiology of crippling postoperative adhesions are the purse-string inverting suture and the neglected stump of the meso-appendix. The frequently infected purse-

string suture (accompanying table) would naturally result in adhesions in spite of the most accurately inverted stump of the appendix. Inversion of the stump of the appendix receives undue attention from most operators, relative to the accurate and untraumatic peritoneal coating of other raw surfaces. Most significant to me is my experience with three operable small bowel obstructions, two of which were due to adhesions to the stump of the previously neglected meso-appendix.

INFECTIONS

Inverting Suture.—With an indisputable general asepsis on the part of the surgeon and his assistants, the most frequent source of infection is the suture used to invert the stump of the appendix. The thin walls of the cecum are very easily penetrated by any form of a Lembert suture, which, in order to hold, must include the submucosa. The accurate passage of a medium size intestinal needle down to and through the submucosa only is a feat in dexterity not easily nor uniformly accomplished. It results, in my experience, very frequently in the penetration of the mucous membrane (table).

Appendix Stump.—The next most frequent source of infection is the mucosa in the stump of the appendix. In order to prevent infection from the mucosa it must be sterilized by heat or chemicals. A ligated appendix stump, whether inverted or not, should have the mucosa completely sterilized. Amputation of the appendix with a cautery does not always leave the stump sterile, as proved by the fact that I obtained cultures from the deepest portion of the stump far more frequently than I anticipated. The deepest portion of the mucosa in the appendix stump is frequently overlooked because it is rarely touched by a cautery. It can only be reached by chemicals such as pure phenol.

Crushing Forceps.—Another frequent source of infection is the crushing forceps, which is applied to the base of the appendix for the purpose of allowing the ligature to set firmly and also to prevent hemorrhage. Experience has taught that hemorrhage is not always prevented with the crusher alone. The appended table will prove that the crusher forces bacteria through the coats of the appendix. This will easily result in contamination of the ligature when applied in the crushed groove. This crushed groove also leaves an infected pocket in the cecum if the stump is inverted.

BACTERIOLOGIC EXPERIMENTS

Under the most careful aseptic technic I removed 100 appendixes, crushing the base of the appendix before ligating it and inverting the stump with a purse-string suture. The appendix was carefully ampu-

tated with a cautery, which had a point fine enough to burn out the mucosa almost down to where it was ligated. The amputated ends of the tied purse-string, including the needle, were immediately dropped by me into a sterile tube of bouillon and the crushing forceps was cultured where it had come in contact with the appendix. The mucosa of the amputated stump was scraped in its deepest portion for the purpose of obtaining bacterial contamination. The bacteriologic studies were carried on by Dr. A. S. Rubnitz, pathologist to Wise Memorial Hospital, who reported the growths as indicated in the table. No attempt was made to recognize the exact type of organism present; only a rough classification was adopted, which answers the purpose of this study. Two cultures of spore-bearing bacilli were obtained from the purse-string cultures, and I regret that we did not determine whether or not they were tetanus bacilli. The cultures from the stump of the appendixes, which had been amputated with a fine pointed cautery, were positive for pyogenic growths in five instances out of twenty. In no instance out of twenty could I obtain a culture from the mucosa to which pure phenol had been properly applied. These two experiments are not included in the table.

Eighty-eight per cent. of the purse-string sutures and 24 per cent. of the crushing forceps gave positive cultures. Naturally the question of errors in technic comes up, but I can vouch for the fact that our surgical and cultural technic met at least with the average degree of indisputable asepsis. Of additional confirmation is the fact that not one of the 100 patients indicated any signs of postoperative infection. Two of the patients, who had additional surgery, died unavoidably, but the postmortem examinations showed no signs of infection.

The high percentage of purse-string suture contaminations certainly suggests, granting an indisputable general asepsis, that the needle was avoidably passed too deeply into the walls of the cecum. From a careful observation of other surgeons, I am sure that I penetrated the cecum no more than is done in the average technic applied elsewhere. I endeavored to reach no deeper than the submucosa, using a medium size straight intestinal needle carrying silk the diameter of 000 catgut. It is doubtful if more than a very few surgeons can pass 100 inverting sutures without a most significant percentage of them giving a positive growth in culture mediums. The percentage of contaminated sutures would vary but there would be contamination enough in the hands of all surgeons to prove that this suture can never be ruled out as a possible source of postoperative infection. When a purse-string appendectomy is added to other surgical procedures, it should be kept in mind that it quite likely will be a contaminated step and should be safeguarded in some way to prevent spreading of this contamination.

Culture Report of Purse-String Suture, Needle and Crushing Forceps

Case	Suture and Needle*	Crusher†	Additional Surgery	Results‡
1	Diplococci	Negative	Perineorrhaphy and double salpingectomy	No infection
2	Diplococci	Negative	None	No infection
3	Diplococci	Negative	Left salpingo-oophorectomy	No infection
4	Diplococci	Negative	Cholecystectomy	No infection
5	Diplococci	Colon bacillus	Cholecystectomy and gastro-enterostomy	No infection
6	Diplococci	Negative	Right salpingectomy	No infection
7	Diplococci	Negative	None	No infection
8	Diplococci	Negative	None	No infection
9	Diplococci	Bacillus subtilis	Cholecystectomy	No infection
10	Diplococci	Negative	None	No infection
11	Diplococci	Negative	None	No infection
12	Diplococci	Diplococcus	None	No infection
13	Diplococcus and colon bacillus	Negative	Perineorrhaphy, uterine fixation	No infection
14	Diplococcus and colon bacillus	Negative	None	No infection
15	Diplococcus and colon bacillus	Negative	Gastro-enterostomy	No infection
16	Diplococcus and motile bacillus	Negative	Dilation and curettage	No infection
17	Bacillus pyocyaneus	Colon bacillus	None	No infection
18	Bacillus pyocyaneus	Colon bacillus	Cholecystectomy	No infection
19	Bacillus pyocyaneus	Negative	Cholecystectomy	No infection
20	Bacillus pyocyaneus	Negative	Panhysterectomy with right tube and ovary	No infection
21	Bacillus pyocyaneus	Negative	Cholecystectomy	No infection
22	Bacillus pyocyaneus	Colon bacillus	Excision of gastric ulcer, gastro-enterostomy	No infection
23	Bacillus pyocyaneus	Negative	Fibromyomectomy of uterus	Died from cardiac failure 8 days later
24	Bacillus pyocyaneus	Negative	Plication of uterine ligaments and perineorrhaphy	No infection
25	Bacillus pyocyaneus	Negative	Cholecystectomy	No infection
26	Bacillus pyocyaneus	Negative	Dilation and curettage, perineorrhaphy, hemorrhoidectomy	No infection
27	Bacillus pyocyaneus	Diplococcus	Cholecystectomy	No infection
28	Bacillus pyocyaneus	Negative	Cholecystectomy	No infection
29	Bacillus pyocyaneus	Small bacillus (?)	Cholecystectomy	No infection
30	Bacillus pyocyaneus	Negative	Double salpingectomy	No infection
31	Colon bacillus	Negative	None	No infection
32	Colon bacillus	Negative	None	No infection
33	Colon bacillus	Negative	None	No infection
34	Colon bacillus	Colon	Right oophorectomy and perineorrhaphy	No infection
34	Colon bacillus	Negative	None	No infection
36	Colon bacillus	Negative	None	No infection
37	Colon bacillus	Negative	Cholecystectomy	No infection
38	Colon bacillus	Negative	Cholecystectomy	No infection
39	Colon bacillus	Colon bacillus	None	No infection
40	Colon bacillus	Negative	Supravaginal hysterectomy	No infection
41	Colon bacillus	Negative	Cholecystectomy	No infection
42	Colon bacillus	Colon bacillus	None	No infection
43	Colon bacillus	Negative	None	No infection
44	Colon bacillus	Negative	Supravaginal hysterectomy, removal Meckel's diverticulum, hemorrhoidectomy, perineorrhaphy	No infection
45	Colon bacillus	Staphylococci	None	No infection
46	Colon bacillus	Negative	None	No infection
47	Colon bacillus	Negative	Cholecystectomy	No infection
48	Colon bacillus	Negative	Cholecystectomy	No infection
49	Colon bacillus	Negative	Cholecystectomy and removal of stone in common duct	Died of acute fatty degeneration of liver
50	Colon bacillus	Negative	None	No infection
51	Colon bacillus	Negative	None	No infection
52	Colon bacillus	Colon bacillus	Cholecystectomy	No infection
53	Colon bacillus	Negative	None	No infection
54	Colon bacillus	Negative	Cholecystectomy	No infection
55	Colon bacillus	Negative	Uterine suspension, perineorrhaphy	No infection
56	Colon bacillus	Negative	Cholecystectomy	No infection

* Eighty-eight per cent. of the purse-string sutures showed bacterial contamination.
† Twenty-four per cent. of the crushing forceps cases showed bacterial contamination.
‡ There were no clinical signs of infection in the one hundred operations.

Culture Report of Purse-String Suture, Needle and Crushing Forceps —(Continued)

Case	Suture and Needle	Crusher	Additional Surgery	Results
57	Colon bacillus	Negative	Supravaginal hysterectomy	No infection
58	Colon bacillus	Negative	None	No infection
59	Colon bacillus	Negative	Cholecystectomy	No infection
60	Colon bacillus	Streptococcus	Cholecystectomy	No infection
61	Colon bacillus	Negative	None	No infection
62	Colon bacillus	Negative	Cholecystectomy	No infection
63	Colon bacillus	Negative	Cholecystectomy	No infection
64	Colon bacillus	Negative	Cholecystectomy	No infection
65	Colon bacillus	Negative	Cholecystectomy	No infection
66	Colon bacillus	Negative	Bilateral salpingectomy, oophorectomy	No infection
67	Colon bacillus	Negative	None	No infection
68	Colon bacillus	Negative	None	No infection
69	Colon bacillus	Colon bacillus	Resection of colon, gas tube through stump of appendix, purse-string suture	No infection
70	Staphylococcus	Negative	Cholecystectomy	No infection
71	Staphylococcus	Negative	Cholecystectomy	No infection
72	Staphylococcus	Negative	Cholecystectomy	No infection
73	Staphylococcus	Negative	None	No infection
74	Staphylococcus	Staphylococcus	Panhysterectomy	No infection
75	Staphylococcus	Negative	Curettage and resection Bartholin gland	No infection
76	Staphylococcus	Negative	None	No infection
77	Staphylococcus	Negative	None	No infection
78	Staphylococcus	Negative	Cholecystectomy	No infection
79	Staphylococcus	Negative	Cholecystectomy	No infection
80	Staphylococcus	Staphylococcus	Dilation and curettage	No infection
81	Small bacillus	Negative	None	No infection
82	Small bacillus	Negative	Cholecystectomy	No infection
83	Small bacillus	Negative	Pyloroplasty	No infection
84	Spore-bearing bacillus	Negative	Removal left tube and ovary	No infection
85	Spore-bearing bacillus	Negative	Gastro-enterostomy	No infection
86	Bacillus subtilis	Negative	None	No infection
87	Bacillus, gram-negative	Bacillus, gram-negative	None	No infection
88	Bacillus (?)	Bacillus (?)	None	No infection
89	No growth	Colon bacillus	Cholecystectomy	No infection
90	No growth	Colon bacillus	Fixation of cecum, uterine suspension, perineorrhaphy, cauterization urethral caruncle	No infection
91	No growth	Colon bacillus	Cholecystectomy	No infection
92	No growth	Colon bacillus	None	No infection
93	No growth	Negative	Cholecystectomy	No infection
94	No growth	Negative	None	No infection
95	No growth	Negative	Cholecystectomy	No infection
96	No growth	Colon bacillus	Cholecystectomy	No infection
97	No growth	Negative	Cholecystectomy	No infection
98	No growth	Negative	Cholecystectomy	No infection
99	No growth	Negative	Right oophorectomy	No infection
100	No growth	Negative	Cholecystostomy	No infection

CONCLUSIONS

1. Pathologic adhesions follow nearly every appendectomy (85 per cent.) and result from trauma, infection and improper peritoneal coating. These are errors in technic and should be looked on as avoidable.

2. Pathologic adhesions are undesirable and should not be looked on with indifference. They are the cause of local pain and tenderness, postoperative constipation and operable or fatal intestinal obstructions.

3. Owing to its greater size, the uncovered mesenteric stump, if not retracting behind the cecum, is as frequent a source of adhesions as the uncovered sterilized appendix stump. Covering the mesenteric stump is a step in technic worthy of consideration.

4. The crushing forceps, particularly of the angiotribe type, frequently leaves an infected crushed groove. This should be taken into consideration during a ligation of the crushed appendix owing to contamination of the ligature. The crushing forceps can always be dispensed with because a silk or catgut ligature sets firmly enough in the uncrushed appendix stump to accomplish its purpose.

5. The mucosa in the stump of the appendix can be entirely sterilized by a proper application of pure phenol. If properly used, it is as germicidal as the cautery and always available. If the appendix stump is not to be inverted, it can generally be so replaced into the peritoneal cavity that, if adhesions do form, only the posterior lateral peritoneum will be attached. The uninverted sterile appendix stump quite likely will not be the greatest source of adhesions if trauma and infection and a neglected meso-appendix stump accompany the technic.

6. The inverting suture is ideal if penetration of the cecal mucosa can be prevented. When this suture becomes most difficult to apply, it should always be dispensed with, providing the stump of the appendix can be sterilized. In applying the inverting suture, it must be kept in mind that it is being passed through the thinnest portion of the gastro-intestinal tract and becomes very frequently contaminated. When a patient exhibits postoperative adhesions or infection, including tetanus, the inverting suture as an etiologic factor must always be kept in mind.

ABNORMAL ARTERIOVENOUS COMMUNICATIONS, ACQUIRED AND CONGENITAL

III. THE EFFECTS OF ABNORMAL ARTERIOVENOUS COMMUNICATIONS ON THE HEART, BLOOD VESSELS AND OTHER STRUCTURES

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ARTERIOVENUS FISTULAS

An Arterviovenus Fistula as a Stimulus to the Development of a Collateral Circulation.—The presence of an arteriovenous fistula constitutes a most powerful stimulus to the development of a collateral circulation. This point, I think, has not been sufficiently stressed. Matas,[1] in advising against too early operations on patients with arteriovenous aneurysms, speaks of the advantage of waiting for the development of a collateral circulation, and he advises encouraging this development by the compression of the proximal artery as advocated by Bramann,[2] Kikuzi,[3] Siago and others. La Roque[4] believes that the collateral circulation becomes impaired in the presence of an arteriovenous fistula. A study of our own cases, as well as of many carefully reported cases in the literature, and the result of our experimental work leave no doubt that an abundant collateral circulation develops around an arteriovenous fistula, greater even than the collateral circulation which develops after the ligation of a main artery. In Case 17, although no pulse could be felt in the paitent's foot previous to operation, Rosenau showed that there was an actual increase in the number of capillaries of the foot. Furthermore, immediately after the excision of this man's fistula, a pulse could be felt in both vessels of the foot; within eight hours, the pedal pulses in the left foot were as strong as those in the right, and the morning after the operation the pulse volume in the left foot was actually larger than that in the right. Similar observations were made in Case 18 (Paper I), while in Cases 19 and 26, in which the patients were operated on very soon after the production of the fistulas, no such observations were made. The congenital cases, Cases 29, 30 and 31, exhibited similar evidences of a large collateral circulation. In Case 31, we observed both at the operation and later, at the dissection of the leg, the large collateral circulation. Matas noted the rapid return

1. Matas, Rudolph: S. Clin. N. A. **2**:1165 (Oct.) 1922.
2. Bramann: Arch. f. klin. Chir. **33**:107, 1886.
3. Kikuzi, cited by Matas in Keen's System of Surgery **5**.
4. La Roque, G. P.: Ann. Surg. **73**:265 (March) 1921.

of a peripheral pulse after the tying of both artery and vein for an arteriovenous aneurysm. In Holman's [5] remarkable case, an absent pulse in the foot could be made to appear and become strong simply by compressing the arteriovenous fistula prior to operation. Kammerer [6] observed that the occlusion of a brachial arteriovenous aneurysm did not stop the radial pulse, and Gerster, commenting on the case, suggested that a sufficient collateral circulation had developed to permit the ligation of both artery and vein. Gehle [7] and Keyes [8] witnessed the return of peripheral pulses within a few hours after the excision of a fistula. Zinninger and myself, by producing arteriovenous fistulas between the femoral vessels in one leg of a dog and ligating the same vessels in the other leg, have proved by roentgen-ray examination that a much more extensive collateral circulation develops on the side of the fistula. In the light of these experiments and of our observations on patients, we are inclined to believe that an arteriovenous fistula is the most powerful stimulus to the development of a collateral circulation. When we consider that the parts peripheral to a fistula are deprived of their allotted blood supply by reason of a shunt, there is little wonder that nature makes a prodigious effort to compensate by the development of other vascular channels.

If our contention is true, then the artificial efforts to promote a collateral circulation in the presence of an arteriovenous fistula are useless, if not actually contraindicated.

The Effect of Arteriovenous Fistulas on the Vessels Involved.—In ten of the reported cases, a more or less marked dilatation of the artery proximal to a fistula was observed. This effect of an arteriovenous aneurysm has been observed by Hunter,[9] Broca,[10] Osler,[11] Matas [1] and many others, and has been admirably studied and investigated by Halsted,[12] Leriche,[13] Callander [14] and Holman.[5]. The artery distal to a fistula is usually contracted and smaller than the normal. However, Callander and Curtis [15] each found four reported cases in which the artery distal to a fistula was dilated. Such an observation was made in

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5. Holman, Emil: Physiology of an Arteriovenous Fistula, Arch. Surg. **7**:64-82 (July) 1923.
6. Kammerer: New York M. J. **51**:532, 1890.
7. Gehle, H.: Berl. klin. Wchnschr. **24**:299, 1887.
8. Keyes, E. L.: Virginia M. Month. **8**:644, 1881-1882.
9. Hunter, W.: Tr. M. Obst. Soc. Phys. London **1**:323, 1857.
10. Broca: Bull. Soc. de chir. de Paris **4**:392, 1863.
11. Osler, W.: Lancet **2**:1248, 1913.
12. Halsted: Tr. Am. Surg. A., 1919.
13. Leriche, René: Bull. et mém. Soc. de chir. **48**:640 (May 13) 1922.
14. Callander, C. L.: Reports Johns Hopkins Hosp. **19**, 1920.
15. Curtis, B. F.: Am. J. M. Sc. **101**:142, 1891.

Case 18, reported in the first paper of this series. This distal dilatation was not marked, and may possibly have been present before the fistula was made (a so-called arterial spindle). Piersol [16] and other anatomists speak of spindles that may occur in an artery just distal to a sharp angle or the point of crossing of a bone like the first rib, and say that they are very frequently observed in the subclavian artery. Everyone knows that the arteries leading into a cirsoid aneurysm (arteriovenous fistulas) become much enlarged. This has been particularly observed in the scalp where, because of the free anastomoses, all the arteries may enlarge as a consequence of a cirsoid aneurysm. The veins involved in these anastomoses and those subjected to increased pressures, as a result of the fistula, become dilated; the dilatation of the feeding artery or arteries to a simple angioma is probably fundamentally the same as the dilatation of the arteries proximal to an arteriovenous fistula or cirsoid aneurysm. While the etiology of the dilated veins seems evident, nobody has yet offered an adequate explanation for the dilatation of the proximal arteries or even of the dilatation of the heart. Holman [8] has made a most valuable contribution to this subject in a recent number of the ARCHIVES OF SURGERY but has, I think, failed to consider the importance of the degenerative changes in the walls of the proximal arteries. It would be unusual if a simple handling of an increased volume of blood by the proximal vessels did not lead to an hypertrophy and strengthening of their walls.

In addition to dilatation, the arteries proximal to arteriovenous fistulas undergo marked degenerative changes; their walls become thin; muscular layers atrophy, and the amount of elastic tissue becomes less.[17] It has been repeatedly observed that the arteries leading to a cirsoid aneurysm or an arteriovenous fistula may be as thin-walled as veins and that they may even rupture. These degenerative changes bring about a dilatation beyond all proportion to the size of the fistula. If these changes are considered together with Holman's proof of the increased work done by the proximal artery or arteries, the reason for the dilatation perhaps becomes easier to understand. But the explanation of the degenerative changes is difficult, unless Thoma's idea, that a normal pulse pressure is essential to the integrity of the arterial wall, is accepted. Ney [18] and others have shown that there is a marked decrease in the pulse pressure of an artery proximal to a fistula. Bourge's idea was somewhat the same, for he attributed the nutritive

16. Piersol: Textbook of Anatomy.

17. These changes are similar to those (observed by Halsted and myself) that occur in the walls of an artery distal to a partially occluding band, or the subclavian artery distal to a cervical rib.

18. Ney, E.: Arch. f. klin. Chir. **100**:531, 1912.

alterations in the wall of the dilated artery to functional inertia brought on by diminished pressures. A vessel supplied with elastic tissue to the extent that a large artery is supplied may find it difficult to get nourishment when its pulse pressure is so markedly diminished as it is in the vicinity of a fistula.

The occurrence of a true aneurysm in the dilated artery proximal to an arteriovenous fistula has been observed a few times. Curtis (1891)[18] reported having found a small, true aneurysm in the femoral artery in a case of popliteal arteriovenous fistula. Osler (1905)[19] exhibited before the Johns Hopkins Medical Society a patient who probably had a true aneurysm of the iliac artery, following a long standing fistula between the femoral vessels.

> The man—now 31 years of age—had, in his eleventh year, received a knife wound just above the right knee. This was soon followed by a swelling of the calf of the leg and, a little later, pulsation was noticed along the femoral artery with the development of a swelling in that region. The patient's health had remained good, and he was exceptionally vigorous except for some disability in the right lower limb and for attacks of hemorrhage from varicose veins in the lower leg. Along the outer thigh reaching from the lower ribs to the foot, ran huge, tortuous varicose veins, and the whole right leg was enlarged. Thrombi were palpable in the veins, some of them organized and a few probably calcified. There was a pulsating swelling in Scarpa's space and along the femoral artery. Over this, a thrill was felt most intensely about the middle of the thigh. In the abdomen was another pulsating tumor 8 inches (20.3 cm.) across and occupying most of the hypogastrium and right iliac fossa. The pulsation here, too, was expansible in character and over it a thrill could easily be felt. The abdominal tumor was thought by Dr. Osler to be a large venous sinus associated with the enormous venous dilatation above a traumatic arteriovenous aneurysm. Its origin was, however, not perfectly clear, and, so far as he knew, there were no other cases like this one in the literature.

DaCosta (1914)[20] reported a brachial arteriovenous fistula with a small true aneurysm 1½ inches (3.7 cm.) proximal to it. The presence of this true aneurysm made him decide to excise the fistula. In this case, it is possible that there had been some trauma of the vessel at the site of the true aneurysm, although he looked carefully and could find no evidence of it. Osler's famous case of axillary arteriovenous aneursysm, which he followed for a period of sixteen years, was a case of what amounted to a true aneurysm proximal to the fistula. Indeed, when the patient died, the pathologist removed the enormously dilated artery and vein, but failed to include with the specimen the fistula, which was more distal. For this reason, as Halsted has pointed out, a drawing of the specimen is often labeled in the literature as an example of a healed

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19. Osler, W.: Bull. Johns Hopkins Hosp. **16**:146, 1905.
20. DaCosta: St. Paul M. J. **16**:310, 1914.

arteriovenous fistula. Case 10 (Paper I) is, so far as I can learn, a unique observation. Six years after Halsted restored the vessels for an arteriovenous aneurysm in Hunter's canal, the patient required an amputation because of a large true aneurysm in Scarpa's triangle. At the time of his operation, the femoral artery was hugely dilated. Small aneurysms have not infrequently been observed in the dilated arteries proximal to a cirsoid aneurysm. Holmes [21] states: "In the more severe

Fig. 1 (Case 10, Paper I).—*A*, femoral arteriovenous fistula of thirty years' duration; *B*, *C* and *D*, the artery markedly dilated. After a cure of the fistula by restoration of the vessels, a simple aneurysm developed at *B*, causing gangrene of the leg and necessitating amputation. This occurred six years after the operation on the fistula.

cases the artery is greatly dilated, and presents unequal, saccular pouches, which are in fact so many true aneurysms." Wright (1831),[22] Mynter (1890)[23] and others have made similar observations. In Case 31 (Paper I), there were small true aneurysms on each branch of the anterior

21. Holmes: System of Surgery.
22. Wright, T. H.: Am. J. M. Sc. **9**:90, 1831.
23. Mynter, Herman: Ann. Surg. **12**:93, 1890.

tibial artery before it entered the tibia, where there were free anastomoses between the arteries and veins.

The thin walled arteries and veins of cirsoid aneurysms tend to rupture. As a result of this, new fistulas might easily be established. This would explain the numerous fistulas in cirsoid aneurysms and, also, the rapid growth of some of these lesions following trauma or the strain of pregnancy. Brämann suggests that, in cirsoid aneurysms, the

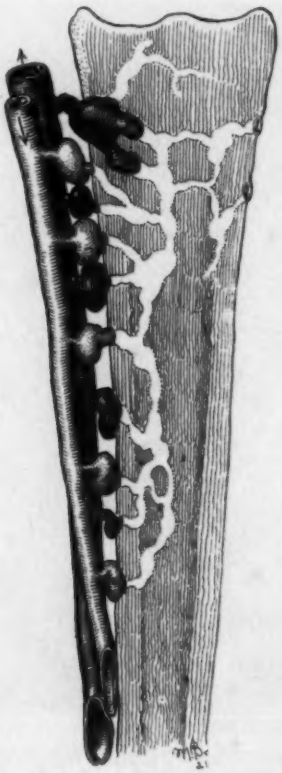

Fig. 2.—(Case 31, Paper I).—Cirsoid aneurysm in the tibia. The small aneurysms on the branches of the anterior tibial artery just before they enter the bone, where there are free arteriovenous anastomoses, may be noted.

vessel walls give way and that new fistulas are constantly forming. Indeed, it would be quite surprising if the thin walled, closely packed, pulsating vessels of a cirsoid aneurysm did not spontaneously break into each other.

To a certain extent, the mechanism of the dilatation of the vessels in an arteriovenous aneurysm works in a vicious circle; as the vessels dilate so does the fistula that is directly responsible for their dilatation.

Effects of An Abnormal Arteriovenous Communication on the Heart.—It is due mainly to the writings of Halsted, Matas, Leriche, Callander and Holman that the evil effects of an abnormal arteriovenous communication on the heart are now becoming pretty generally known. For a long time, it has been known that congenital communications between the various chambers of the heart, the persistence of a patent ductus arteriosus, and the spontaneous or experimental communication between the aorta and vena cava frequently lead either to marked cardiac hypertrophy and dilatation or to the rapid death of the patient. In the experiments of Carrel [24] and Bernheim, the production of fistulas between the aorta and the vena cava or, as in Holman's work, the simultaneous production of two fistulas in the neck, was often followed by sudden death. In spite of this knowledge, it has taken the profession a long time to establish a cause and effect between arteriovenous fistulas, in vessels smaller than the aorta, and the cardiac disturbances they produce. So often we remain blind to the insidous conditions that shorten the duration of human lives. Although Osler for years followed two cases of arteriovenous aneurysms (one axillary, the other femoral) in which the patients died from cardiac disease at the early ages of 29 and 46, he was never, unless possibly shortly before his death, convinced of the causal relationship existing between the two conditions; and for a long time he counseled against operations on arteriovenous aneurysms. However, the effect of arteriovenous fistulas on the heart is now well known, and numerous cases in which a dilated and hypertrophied heart has practically returned to its normal condition following the cure of a fistula have been reported (Leriche, Holman and others). I have been able to show experimentally on dogs that a fistula between the carotid artery and the external jugular vein may lead to an hypertrophied and dilated heart. In the cases reported in Paper I, Cases 10, 13, 14 and 17 were associated with a cardiac hypertrophy.

Although Holman, Carrel, Matas and others have offered very plausible explanations for the cardiac changes, I do not believe that the mechanism is yet entirely understood. The sudden deaths that follow a fistula between the aorta and vena cava, and occasionally the larger trunk vessels, may likely be due to an overloading of the right side of the heart, but the cardiac hypertrophies and dilatation that develop slowly after more remote arteriovenous fistulas are not so easily explained. In such cases, the cardiac changes are always associated with a dilatation of the proximal portion of the involved artery, and, in severe cases, this dilatation extends all the way back to the heart. Even in long standing cases, we have failed to detect any cardiac changes

24. Carrel, Alexis: Results of the Transplantation of Blood Vessels, Organs and Limbs, J. A. M. A. **51**:1662 (Nov. 14) 1908.

whenever the proximal artery has not been enlarged. In an experiment performed by Holman and myself, bilateral arteriovenous fistulas in the neck of a dog did not produce, in two years, any cardiac hypertrophy and dilatation. When the animal was killed, it was found that there was no proximal dilatation of the arteries (Fig. 3). Indeed, it would seem that

Fig. 3.—Bilateral arteriovenous fistula in the neck of a dog. The operation was performed by Holman. Dogs rarely survived this operation; in this instance, the animal was killed after two years. The failure of the proximal carotid vessels to dilate may be observed; the heart was normal.

the effect of an acquired arteriovenous fistula on the proximal portion of the involved artery might be used as a good index of the seriousness of the lesion, so far as the heart is concerned.

An interesting observation has been the absence of any cardiac complications associated with our congenital abnormal communications and the cirsoid aneurysms. Although the proximal arteries dilate tremendously in cirsoid aneurysms, cardiac changes are rarely associated with them. In the very peripheral lesions, as in cirsoids, or in the congenital lesions between even larger vessels (Case 30, Paper I), the heart may be able to adapt itself to the changed vascular bed. Most of these lesions either have been present from birth or have developed in young people.

When a large arteriovenous fistula is present, there is usually a rapid pulse rate. If the fistula is closed, there may be an astonishing drop in the rate (Branham's bradycardiac phenomenon [25]). Matas reported a drop from 80 to 60; Branham, a drop from 80 to 35. Holman has pointed out the fact that the increased rate is largely due to the increased volume of blood that the heart must handle in a given unit of time. During exercise in a normal person, the rapid pulse may be due to the same cause, the dilated capillaries permitting the blood to return more readily to the heart, thus increasing the volume of blood that the heart must handle in a given unit of time. In the case of a fistula, the demand of the part beyond it for a better blood supply may also be a factor in the increasing of the pulse rate. In this connection, it is interesting to note that Matas reports two cases in which a tachycardia developed following restoration of the vessels for an arteriovenous aneurysm. This observation is more easily understood if we bear in mind that, in the part beyond a fistula, there is a marked increase in the number and size of the capillaries, and also of the collateral arteries about the fistula. With the vessels restored, the blood might for a time find even a more ready return to the heart than it did when the fistula was present. Likewise, the bradycardia resulting from the closure of the main vessels involved in a fistula might be due to the greatly increased vascular bed being thrown into use and not being subjected to a strong head of pressure. The tachycardia following the restoration of the vessels and the bradycardia following the excision of the vessels for an arteriovenous aneurysm do not persist longer than a week or ten days. In this time, adaptation to the new use of the large vascular bed occurs. Of the cases reported in this series of papers, Cases 2 and 5 exhibited a bradycardia following the excision of the fistulas.

The Effect of Abnormal Arteriovenous Communications on the Blood Pressure.—Case 2, Paper I, showed a definite rise in the general blood pressure following excision of the vessels along with the fistulas. Holman, Callander and others have observed similar rises in blood pressure occurring after the simple occlusion, by pressure, of the main vessels at the point of fistula. It is interesting to note that the variation

25. Branham, cited by Matas, Rudolph: S. Clin. N. Am. **2**:1165 (Oct.) 1922.

in the blood pressures of Holman's patient were not so marked after a restoration of the vessels as before operation, when the vessels were occluded by pressure. I have not found any other similar observations. Here, again, these blood pressure changes resulting from excision or the restoration of the vessels for an arteriovenous aneurysm may be dependent on the amount of head pressure necessary for the proper function of the vascular bed beyond the site of the fistula.

Impairment of the Circulatory Balance.—There is a marked impairment of the circulatory balance in parts supplied by vessels involved in

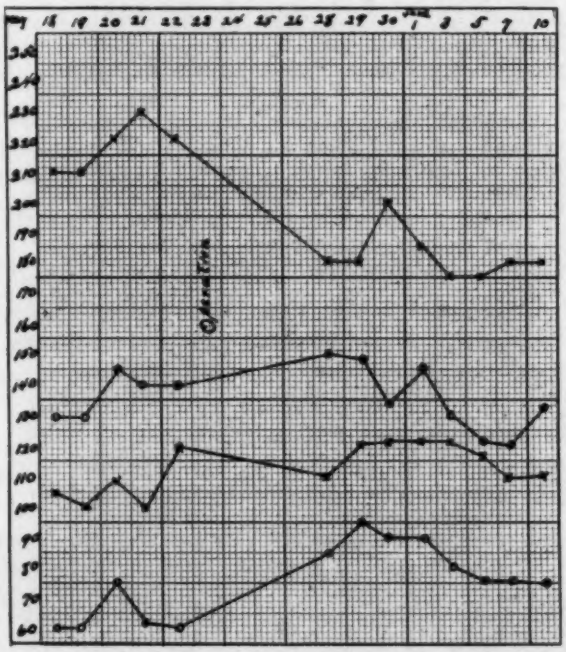

Fig. 4 (Case 17, Paper I).—Blood pressures in the right arm and leg before and after operation, to show the result of the excision of the fistula on the general blood pressure. Reading from above down, the curves represent: systolic, right leg; systolic, right arm; diastolic, right leg; diastolic, right arm.

an arteriovenous aneurysm. The rise in venous pressure and the fall in arterial pressure distal to the fistula contrive to disturb the normal circulatory balance. There is almost certainly an increase in the capillary pressure, for Danzer and Hooker have shown that venous compression causes an increase in the capillary pressure. Cases 1, 2, 4, 6, 8, 12 and 13, Paper I, illustrate very well this circulatory embarrassment peripheral to the fistulas. It is very interesting to compare the efforts at circulatory adaptation to various positions of the affected limb with those of the sound limb.

Observations on Surface Temperature.—In arteriovenous aneurysms the surface temperature in the region of the lesion is elevated, while in the part distal to the lesion it is lowered. Observations of this nature were made in Cases 1, 4, 12 and 14, Paper I. Following the cure of the aneurysm, even when the vessels are excised, the surface temperature of the distal part often rises several degrees higher than that of the corre-

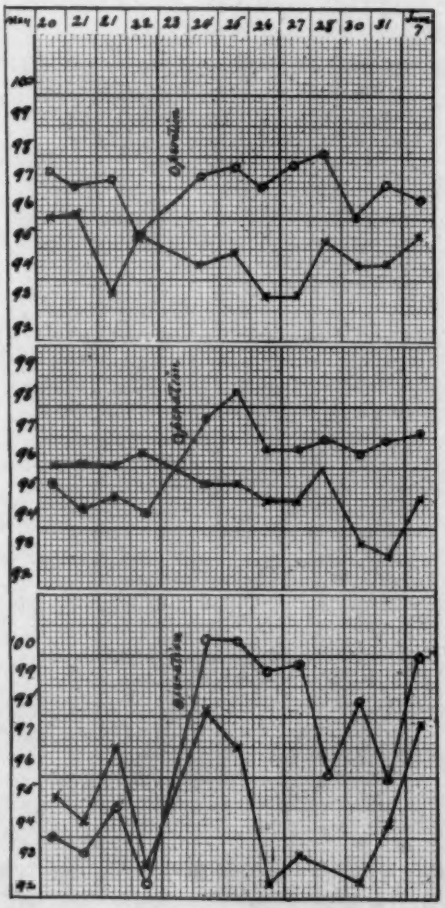

Fig. 5 (Case 17, Paper I).—Effect of the arteriovenous aneurysm on the surface temperature of the left leg, before and after extirpation of the fistula. Reading from above down, the curves represent: left thigh; right thigh; right calf; left calf; right foot; left foot. The immediate rise in temperature of the foot and calf following operation may be seen. They became warmer than the normal, or right, leg; before operation, they were colder.

sponding normal part (Fig. 5). These variations in temperature are directly due to the activity of the circulation or the amount of arterial blood traversing the region. About the fistula, the arteries and veins

become dilated and carry arterial blood, and there is an increase in surface temperature; beyond the fistula, there is a decreased blood supply and a consequent drop in the surface temperature. Following the cure of the fistula and an active use of the enlarged vascular bed beyond it, the surface temperature of the distal part for a time rises above normal, while the surface temperature in the region of the fistula slowly drops to normal.

Fig. 6 (Case 31, Paper I).—Cirsoid aneurysm in the tibia. The increased length of the bone and the unusual roentgen-ray picture is shown.

Increased Length of the Involved Part.—That vascular lesions such as angiomas, cirsoid and arteriovenous aneurysms may lead to an increased length of the involved part has long been known. In DaCosta's textbook of surgery there is a beautiful example of an increased length of the leg brought about by a cavernous angioma. The congenital cirsoid aneurysm in Case 31 (Fig. 6) had caused the affected leg to become 6 cm. longer than the normal leg. We have not noted an increase in the length of the limb in our cases of arteriovenous aneu-

rysms, but this is probably because the lesions have all occurred in adult people whose epiphyses were ossified. Callander, however, collected several instances in which an arteriovenous aneurysm in children resulted in an increased length of the limb. Such cases were reported by Giraldes,[26] Cordonnier,[27] Davis,[28] Hewett [29] and Franz.[30] Other affections during adolescence, such as osteomyelitis, may lead to an increased length of a limb. One would scarcely expect an abnormal arteriovenous communication to increase the length of a fully grown bone.

Instances of shortening due to an angioma (venous) have not, so far as I know, been reported. For that reason, an abstract of the case of a patient seen by me, Dec. 10, 1923, is given.

The girl, aged 13, was born with a bluish discoloration of the heel and outer aspect of the foot and the posterior part of the leg all the way to the buttock. Very little attention was paid to this condition until, at the age of 4, the child developed trouble with the left knee. As a result, she was given a series of nine or ten roentgen-ray treatments without any beneficial effect. Since that time, she had had numerous attacks of disability in the left knee, which often necessitated her staying off it from several days to two or three weeks. There was no history of chills, fever or vomiting associated with these attacks; nor do they follow as a result of localized infection, such as tonsillitis. It had been noted by her friends that she limped and that the left leg was a little shorter than the right.

The examination showed that the entire left leg and foot were smaller than the right. The left leg was much paler than the right, except at points where the angiomatous condition came to the surface.

The following measurements were made: Left tibia, 34.25 cm.; right tibia, 35.25 cm. Left femur from trochanter to condyle, 35.5 cm.; right femur from trochanter to condyle, 39.25 cm. Anterior superior spine to internal malleolus, left, 81 cm.; right, 82.5 cm. Circumference of calf, left, 29 cm.; right, 32 cm. Left knee, 28.5 cm.; right knee, 31.25 cm. Left thigh (measuring 9½ inches [24 cm.]) above knee, 40 cm.; right thigh (measuring 9½ inches [24 cm.]) above knee, 44 cm. Length of sole of foot, left, 22.5 cm.; right, 23.5 cm.

A very interesting point was that the child complained very frequently of being dizzy when she assumed a standing position after lying down. This is slightly present now on examination. It is very likely that when she stands up suddenly a great deal of blood is shunted into the angiomatous area, so that the dizziness is due to anemia of the brain. This is a very remarkable case in that the angioma has resulted in a lack of development in the left leg. In nearly all cases reported in the literature and in my own observation the reverse has been true.

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26. Giraldes: Bull. Soc. anat. de Paris **29**:298, 1854.
27. Cordonnier, T.: These de Paris, 1864, No. 57.
28. Davis, G. G.: Tr. Philadelphia Acad. Surg. **17**:212, 1915.
29. Hewett, Prescott: Lancet **1**:146, 1867.
30. Franz: Arch. f. klin. Chir. **75**:572, 1905.

Among other effects of abnormal arteriovenous communications which were noted in our series of cases, but which need not be discussed at length, were: a marked angiomatous condition in the region of the fistula (Cases 17, 30, 18 and 29, Paper I); increased pigmentation of the skin distal to the fistula (Cases 17 and 19, Paper I); ulceration with serious hemorrhage distal to the fistula (Cases 17 and 19, Paper I); marked edema of the arm (Case 18, Paper I); headaches, dizziness, diplopia; annoyance of the thrill and bruit, exophthalmos, ophthalmoplegia—

Fig. 7 (Case 18, Paper I).—Left subclavian arteriovenous aneurysm of six months' duration; the dilated veins and the edema of the arm may be seen. There was telangiectasis about the clavicle.

paralysis of the sixth nerve frequently persists after a cure of the intracranial fistula (Cases 16 and 29, Paper I); calcification of the vessels at the site of fistula (many cases, but notably Cases 10 and 14, Paper I); muscular atrophy, parasthesias, physical disability, thickening of the subcutaneous connective tissue (several cases); nerve disturbances other than those caused by direct injury to the nerves at the time of the production of the fistula (Case 19, Paper I). Case 19 exhibited a glove

type of anesthesia associated with subjective sensations and a partial muscular paralysis of the hand and arm. Very likely, as it has been suggested by Captain Burrows,[31] these disturbances were due to the effect of ischemia on the peripheral nerves. As to the cause of this ischemia it is interesting to quote from Leriche:

When the nerves have not been disturbed, we call it ischemic paralysis, giving to this appellation an entirely different sense from that which we have in mind for the isolated contracture of the flexors of Volkmann. In the cases

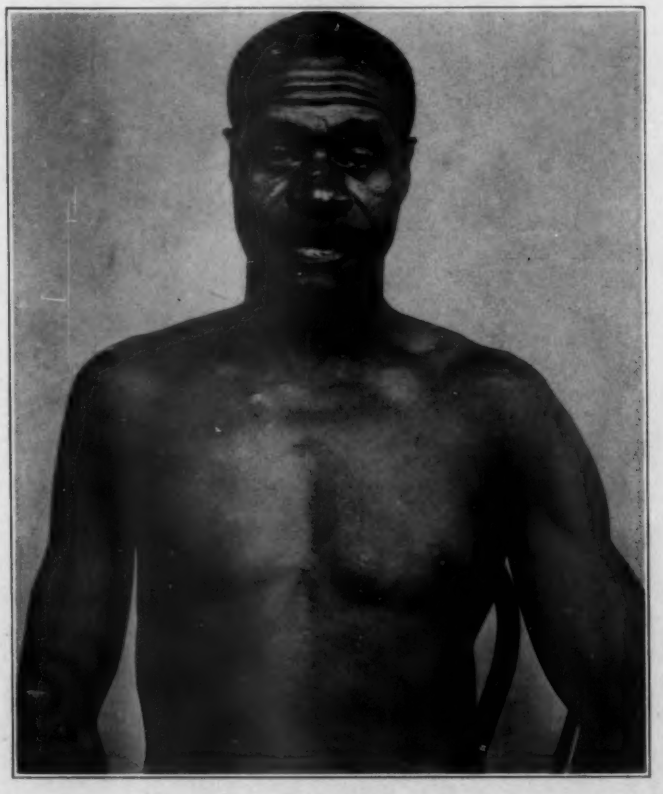

Fig. 8 (Case 19, Paper I).—Right subclavian arteriovenous fistula of sixteen days' duration; atrophy of the arm. There was marked motor weakness but sensation was undisturbed; the nerves were not divided by the injury.

described by MM. Dejerine and Tinel there is rather complete motor paralysis with the reaction of degeneration, yet the nerves were not divided. The paralysis coincided with an edematous infiltration of the hand with marked vasomotor disturbances which lead to true fibrous transformation of the hand. At the end of some weeks the edema begins to diminish, the tendons and aponeuroses are ensheathed in a veritable fibrous envelop; the muscles, already

31. Burrows, cited by Makins in Gunshot Injuries of the Blood Vessels.

hard and tense, retract and take on a ligneous consistency. In this picture is seen the mark of the sympathetic; and in doing sympathectomy in these cases, M. Heitz and I have seen vasomotor disturbances disappear, trophic disturbances improve, the tendons and the muscles become on palpation sensibly more supple, and the muscles execute slight movements. In one case, although before operation there had been complete degenerative reaction, four months after operation we observed a very definite amelioration of the electric reactions, and we are hoping for a marked functional recuperation.

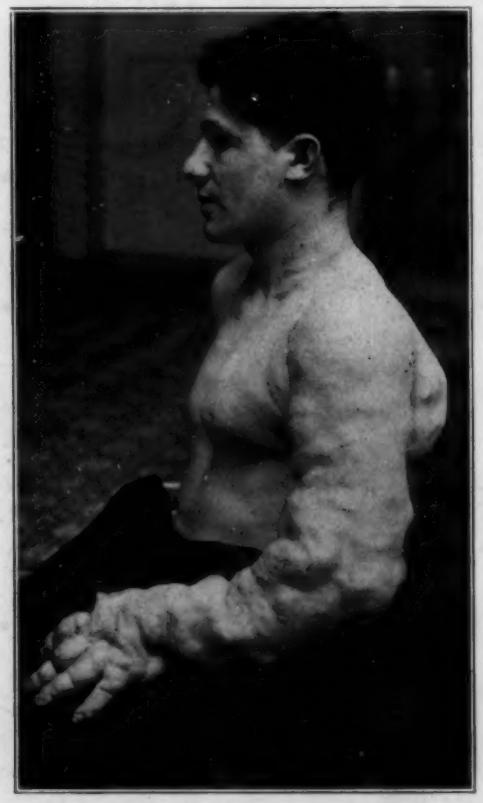

Fig. 9.—Large venous angioma of the arm and shoulder.

The irritation of the perivascular sympathetic nerves, due to the arteriovenous fistula, may produce a constant contraction of the terminal arteries, and thus not only explain these atypical paralyses but also, in a measure, help to explain the generally poor circulation distal to an arteriovenous aneurysm. After complete excision of the artery and vein in Cases 17 and 18, the peripheral arteries became for a time actually larger than normal and pulsated well.

Effect of an Arteriovenous Fistula on the Circulation of the Part Beyond It.—There is abundant clinical and experimental evidence which

indicates not only that an arteriovenous fistula does not improve the circulation to the part beyond it but also that, on the contrary, it actually embarrasses it. In patients, the frequent occurrence of cyanosis, lowered surface temperature, edema and ulceration, and the occasional occurrence of intermittent claudication, gangrene or paraplegia as the result of a fistula between large arteries and veins speak strongly for the deleterious effect of a fistula on the circulation of that part supplied by the vessels involved. The experimental work of Horsley, myself and others has led to the conclusion that, in dogs, an arteriovenous fistula between large

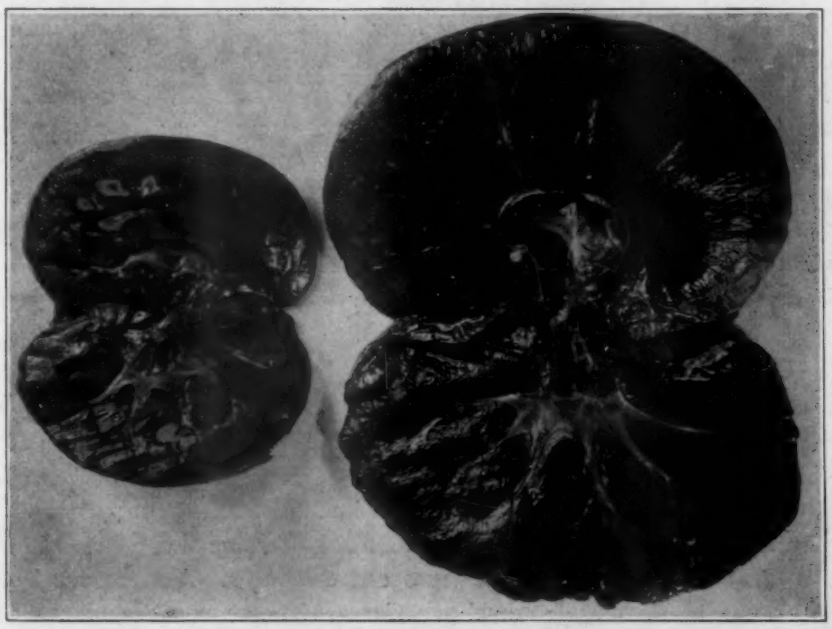

Fig. 10.—The effect on a kidney six days after its circulation had been reversed: the normal kidney on the left; the kidney with a reversed circulation on the right. It is almost completely necrotic.

vessels embarrasses the circulation of the part beyond it. In the immediate vicinity of an arteriovenous fistula there is a definite improvement of the circulation. This is evidenced by the increased local temperature and the development of an angiomatous condition, the vessels of which are filled with arterial blood. This is beautifully illustrated in the case of the cirsoid aneurysms. It is conceivable that an arteriovenous fistula made in the region that one wishes to treat might do some good. On the other hand, it would seem mere folly to expect any benefit from a fistula made between large vessels far removed from the part you are trying to help.

I am aware that quite a few cases of Raynaud's disease have been helped by the making of arteriovenous fistulas between the vessels supplying the involved part. In the light of our present knowledge with respect to the perivascular sympathetics, it is more reasonable to suppose that the sympathectomy performed at the time of making the fistula has been most responsible for the good results. Besides the sympathectomy, another factor that may help to counterbalance the evil effects of a fistula in Raynaud's disease is the stimulating effect that a fistula has on the development of a collateral circulation.

Effect of a Complete Reversal of the Circulation.—I have not been successful in nourishing a part by a complete reversal of the circulation. I have performed numerous experiments on the kidneys of dogs; in no instance has the kidney survived after its circulation has been completely reversed (Fig. 10). Furthermore, the amount of pressure necessary to force fluid through the vascular bed of the kidney in the reversed direction is many times greater than the amount of pressure required to force the fluid in the normal direction. Although Carrel succeeded in having the thyroid gland live after reversing its circulation, it must be borne in mind that this organ will live as a free transplant.

CONCLUSIONS

1. An arteriovenous fistula is a powerful stimulus to the development of a collateral circulation, much greater even than is the stimulus of ligating the vessels.

2. A fistula between artery and vein leads to marked changes in the vessels; the arteries proximal to the fistula become dilated and thin walled, and often show marked degenerative changes. A true aneurysm may form in an artery proximal to a fistula. The veins dilate, and their walls may become thickened.

3. A fistula between large vessels may lead to grave cardiac disturbances or even to sudden death.

4. The circulation of a limb distal to a fistula is usually markedly impaired, even though there is an increase in the capillary bed.

5. The surface temperature distal to a fistula is lowered, while after extirpation of the fistula it may be several degrees higher than it is normally.

6. Arteriovenous or cirsoid aneurysms situated in the extremity of a growing individual may cause a considerable increase in the length of that extremity.

7. In our experiments, a kidney does not live after a complete reversal of its circulation.

EPITHELIOMA OF CAVITIES AND INTERNAL ORGANS OF THE HEAD AND NECK*

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ROCHESTER, MINN.

In this, the last of a series of articles devoted to the study of epitheliomas, the same general plan has been followed as in the preceding papers.[1] The cases of epithelioma have been divided into eight groups from the standpoint of location: (1) the tongue; (2) the inside of the cheeks and lips, gums, floor of mouth, and so forth; (3) the tonsil; (4) the pharynx, and hard and soft palate; (5) the larynx; (6) the esophagus; (7) the inside of the nose, accessory nasal sinuses, nasopharynx and mucous membrane of orbit, and (8) cases in which the primary lesion could not be located.

In grading the degree of malignancy in this series of cases as in my previous cases, cell differentiation plays the important part; that is, if about three-fourths of the epithelioma was differentiated epithelium and one-fourth undifferentiated, it was graded 1; if the differentiated and undifferentiated epithelium were about equal, it was graded 2; if the undifferentiated epithelium formed about three-fourths of the growth, and the differentiated about one-fourth, it was graded 3, and if there was no tendency to cell differentiation it was graded 4 (Figs. 1 to 10). The number of mitotic figures and the number of cells with single large deeply staining nucleoli play an important part in the grading. The epitheliomas grew from protective epithelium similar to that found on the lip, cervix and vagina. Therefore, keratin will represent complete cell differentiation, which is manifested by pearly body formation, and the large flat squamous cells with small nuclei, partial differentiation.

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* From the Section on Surgical Pathology, Mayo Clinic.

* Read before the Midwest Section of the American Laryngological, Rhinological and Otolaryngological Society, Denver, Feb. 2, 1924.

1. Broders, A. C.: Squamous-Cell Epithelioma of the Lip: A Study of Five Hundred and Thirty-Seven Cases, J. A. M. A. **74**:656-664 (March 6) 1920; Squamous-Cell Epithelioma of the Skin, Ann. Surg. **73**:141-160 (Feb.) 1921; Epithelioma of the Genito-Urinary Organs, Ann. Surg. **75**:574-603 (May) 1922.

As I stated in the article on epithelioma of the genito-urinary organs, an epithelioma may be relatively small and of an average degree of malignancy, but its location may make its complete extirpation, with the regional lymph nodes, almost impossible. The epitheliomas of the esophagus (Group 6) were all inoperable, mainly on account of their location. However, epitheliomas of this group are not only inaccessible from a surgical standpoint, but also have a high average of malignancy.

Fig. 1.—Grade 1 epithelioma of the cheek.

The consideration of these cases may be said to be simple and compound, since the groups are discussed individually as well as collectively. For example, if one wishes to compare the end-results in cases of epithelioma of the tongue in Group 1, with epithelioma of the cheeks, gums, and so forth, in Group 2, it is easily accomplished, since the groups are considered from exact standpoints, such as age, duration of lesion, size of lesion, degrees of malignancy, with metastasis, without metastasis, without removal of regional lymph nodes and salivary glands, good result, poor result and duration of life after operation.

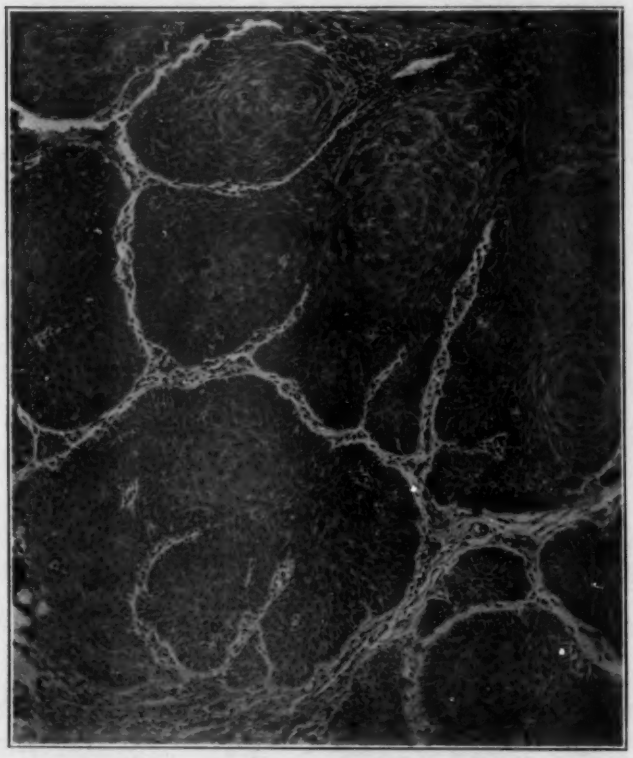

Fig. 2.—Grade 1 epithelioma of the cheek, slightly more malignant than that shown in Figure 1. The pearly bodies are not well defined, but the cells show a rather marked keratinization.

Fig. 3.—Grade 2 epithelioma of the tongue.

Fig. 4.—Growth shown in Figure 3; slightly more malignant than that shown in Figure 2.

Fig. 5.—Grade 2 epithelioma of the larynx.

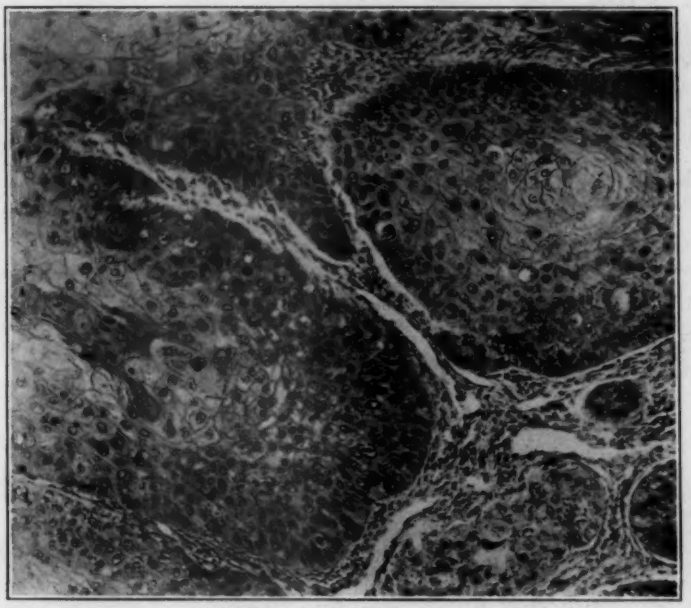

Fig. 6.—Growth shown in Figure 5; slightly more malignant than that shown in Figure 3. Pearly bodies are not in evidence, but the large flat cells with small nuclei are quite numerous.

Fig. 7.—Grade 3 epithelioma of the external jugular lymph node secondary to epithelioma of the larynx; numerous undifferentiated cells, also areas of differentiated cells, which indicate a tendency of the growth to check itself.

Three Hundred Sixty-Two Cases of Epithelioma of Cavities and Internal Organs of Head and Neck (18.1 Per Cent. of 2,000 Cases of General Epithelioma) from Nov. 1, 1904, to July 22, 1915

	Number	Per Cent.
Males	322	88.96
Females	40	11.04
Family history of malignancy	34	9.39

	Youngest, Years	Oldest, Years	Average, Years
All groups	20	81	54.38
Group 1 (Tongue)	30	75	52.22
Group 2 (Gums, inside of cheeks and lips, floor of mouth, etc.)	32	81	56.72
Group 3 (Tonsil)	20	70	48.23
Group 4 (Pharynx, hard and soft palate)	38	76	53.52
Group 5 (Larynx)	32	67	52.84
Group 6 (Esophagus)	31	64	49.66
Group 7 (Nose and accessory sinuses, nasopharynx and conjunctiva)	27	77	53.96
Group 8 (Primary lesion not determined)	46	65	55

Occupation (Males)	Patients	Per Cent.
Farmer	107	34.51 of 310
Merchant	35	11.29 of 310
Laborer	19	6.12 of 310
Salesman	12	3.87 of 310
Lawyer	9	2.9 of 310
Railroad employee	8	2.58 of 310
Butcher	6	1.93 of 310
Saloon keeper	6	1.93 of 310
Miner	6	1.93 of 310
Blacksmith	5	1.61 of 310
Carpenter	5	1.61 of 310
Hotel keeper	5	1.61 of 310
Bookkeeper	4	1.29 of 310
Lumberman	4	1.29 of 310
Painter	4	1.29 of 310
Real estate	4	1.29 of 310
Other occupations each below 1 per cent.	71	22.90 of 310

	Patients	Per Cent.
History of syphilis	25	12.50 of 200
History of syphilis in patients with epithelioma of the tongue	17	31.49 of 54
Previous lesion at site of cancer (crack, leukoplakia, ulcer, wart, etc.)	120	33.14
Bad teeth	73	20.16
Location of the lesion (Fig. 11)		
Group 1 (Tongue)	78	21.54 of 362
Group 2 (Gums, inside of cheeks and lips, floor of mouth, etc.)	171	47.23 of 362
Group 3 (Tonsil)	17	4.69 of 362
Group 4 (Pharynx, hard and soft palate)	17	4.69 of 362
Group 5 (Larynx)	25	6.90 of 362
Group 6 (Esophagus)	12	3.31 of 362
Group 7 (Nose and accessory sinuses, nasopharynx and conjunctiva)	32	8.83 of 362
Group 8 (Primary lesion not determined)	10	2.76 of 362

	Longest, Years	Shortest, Years	Average, Years
Group 1 (Tongue)	15	0.08	0.945
Group 2 (Gums, inside of cheeks and lips, floor of mouth, etc.)	10	0.04	1.34
Group 3 (Tonsil)	3	0.125	0.975
Group 4 (Pharynx, hard and soft palate)	4	0.058	0.83
Group 5 (Larynx)	10	0.125	1.55
Group 6 (Esophagus)	9	0.208	2.35
Group 7 (Nose and accessory sinuses, nasopharynx and conjunctiva)	3	0.08	0.587
Group 8 (Primary lesion not determined)	2	0.25	0.775
All groups	15	0.04	1.18

	Size in Cm.		
	Largest	Smallest	Average
All groups	10	0.6	3.6
Group 1	7.5	0.7	2.83
Group 2	10	1	4.14
Group 3	6.0	1.5	2.86
Group 4	6	2	3.33
Group 5	7.5	1	3.31
Group 7	7.5	1.5	3.85

PATIENTS TREATED BEFORE COMING TO THE CLINIC

	Patients	Per Cent.
One or more treatments alone or in various combinations of acids, carbon dioxid, copper sulphate, electricity, osteopathy, paste or plaster, radium, roentgen ray and silver nitrate	42	11.6
Surgical (One or more operations)	67	18.5
Surgical and nonsurgical combined	7	1.93
Treated surgically, nonsurgically or by both methods	116	32.04

OPERATIONS

Group 1:	Patients	Per Cent.
Number	63	80.76 of 78
Excision of one or more groups of regional lymph nodes and salivary glands followed shortly after by one or more excisions with knife, excisions with knife and cautery, or cauteries of primary growth	37	58.73 of 63
Excision of one or more groups of regional lymph nodes and salivary glands followed immediately by excision with knife and cautery, or excision with cautery, or cautery of primary growth.	8	12.69 of 63
Miscellaneous (excision of one or more groups of regional lymph nodes and salivary glands, associated or not with excision with knife or cautery of primary growth, or various other combinations of operations)	18	28.57 of 63
Inoperable condition	13	16.66 of 78
Refused operation	2	2.56 of 78
Group 2:		
Number	130	76.02 of 171
One or more excisions with knife, with knife and cautery, with cautery, or one or more cauteries of primary growth	45	34.61 of 130
Excision of one or more groups of regional lymph nodes and salivary glands followed shortly or some time after by one or more excisions with knife, excisions with knife and cautery, or cauteries of primary growth	31	23.84 of 130
Excision of one or more groups of regional lymph nodes and salivary glands followed immediately by excision with knife, knife and cautery, excision with cautery, or cautery of primary growth	21	16.15 of 130
Miscellaneous (excision of one or more groups of regional lymph nodes or salivary glands, associated or not associated with excision, with knife or cautery of primary growth, or various other combinations of operations)	33	25.38 of 130
Inoperable condition	40	23.40 of 171
Refused operation	1	0.58 of 171
Group 3:		
Number	11	64.70 of 17
Miscellaneous (excision of one or more groups of regional lymph nodes or salivary glands, associated or not with excision with cautery of primary growth, excision of primary growth which includes seven tonsillectomies)	11	100.0 of 11
Inoperable condition	6	35.29 of 17
Group 4:		
Number	9	52.94 of 17
Excision of one or more groups of regional lymph nodes and salivary glands followed shortly or some time after by one excision with knife, one excision with knife and cautery, or one or more cauteries of primary growth	5	55.55 of 9
Miscellaneous (excision of one or more groups of regional lymph nodes and salivary glands, associated or not associated with excision and cautery of primary growth)	4	44.44 of 9
Inoperable condition	8	47.05 of 17
Group 5:		
Number	20	80.00 of 25
Miscellaneous (excision of one or more groups of regional lymph nodes and salivary glands associated or not associated with laryngotomies, one tracheotomy, excision with knife and cautery, excision with cautery, cautery of primary growth which includes ten laryngectomies)	20	100 of 20
Inoperable condition	4	16.00 of 25
Refused operation	1	4.00 of 25
Group 6:		
Inoperable condition	12	100 of 12
Group 7:		
Number	18	56.25 of 32
Miscellaneous (excision of one or more groups of regional lymph nodes and salivary glands, associated or not associated with excision with knife, excision with knife and cautery, or one or more cauteries of primary growth which include seven resections of the superior maxilla)	18	100 of 18
Inoperable condition	14	43.75 of 32
Group 8:		
Number	6	60.00 of 10
Excision of one or more groups of lymph nodes and salivary glands	6	100 of 6
Inoperable condition	4	40.00 of 10

THREE HUNDRED AND SIXTY-TWO CASES OF EPITHELIOMA, GRADED ON A BASIS OF 1 TO 4 ACCORDING TO CELLULAR ACTIVITY

	Grade 1		Grade 2		Grade 3		Grade 4	
	Patients	Per Cent.	Patients	Per Cent.	Patients	Per Cent.	Patients	Per Cent.
All groups	16	4.41 of 362	161	44.47 of 362	145	40.05 of 362	40	11.04 of 362
Group 1	1	1.28 of 78	37	47.43 of 78	36	46.15 of 78	4	5.12 of 78
Group 2	13	7.60 of 171	93	54.38 of 171	59	34.50 of 171	6	3.50 of 171
Group 3	...	.....	1	5.88 of 17	6	35.29 of 17	10	58.82 of 17
Group 4	...	.....	8	47.05 of 17	6	35.29 of 17	3	17.64 of 17
Group 5	1	4.00 of 25	13	52.00 of 25	9	36.00 of 25	2	8.00 of 25
Group 6	...	.....	1	8.33 of 12	10	83.33 of 12	1	8.33 of 12
Group 7	1	3.12 of 32	5	15.62 of 32	16	50.00 of 32	10	31.25 of 32
Group 8	...	.....	3	30.00 of 10	3	30.00 of 10	4	40.00 of 10

LYMPH NODES AND SALIVARY GLANDS REMOVED IN ONE HUNDRED SEVENTY-ONE CASES

	Cases	Per Cent.
Submental lymph nodes	167	97.66 of 171
Submaxillary lymph nodes and salivary glands (one side)	95	54.97 of 171
Anterior cervical lymph nodes (one side)	83	48.53 of 171
External jugular lymph nodes (one side)	78	45.61 of 171
Submaxillary lymph nodes and salivary glands (both sides)	73	42.69 of 171
Superior deep cervical lymph nodes (one side)	71	41.52 of 171
Inferior deep cervical lymph nodes (one side)	71	41.52 of 171
All cervical lymph nodes (one side)	70	40.93 of 171
Anterior cervical lymph nodes (both sides)	15	8.77 of 171
External jugular lymph nodes (both sides)	14	8.18 of 171
Superior deep cervical lymph nodes (both sides)	9	5.26 of 171
Inferior deep cervical lymph nodes (both sides)	8	4.67 of 171
All cervical lymph nodes (both sides)	7	4.09 of 171
Supraclavicular lymph nodes (one side)	4	2.33 of 171
Parotid lymph nodes (one side)	3	1.75 of 171
Total submental lymph nodes	167	97.66 of 171
Total submaxillary lymph nodes	167	97.66 of 171
Total submaxillary salivary glands	167	97.66 of 171
Total anterior cervical lymph nodes	98	57.30 of 171
Total external jugular lymph nodes	92	53.80 of 171
Total superior deep cervical lymph nodes	80	46.78 of 171
Total inferior deep cervical lymph nodes	79	46.19 of 171
Total cervical lymph nodes	107	62.57 of 171
Total supraclavicular lymph nodes	4	2.33 of 171
Total parotid lymph nodes	3	1.75 of 171
Cases in which no lymph nodes or salivary glands were removed	86	33.46 of 257

PATHOLOGIC FINDINGS IN CASES IN WHICH LYMPH NODES AND SALIVARY GLANDS WERE REMOVED

	Cases	Per Cent.
Number	171	66.53 of 257
No metastasis	66	38.59 of 171
Metastasis	105	61.40 of 171
Submaxillary lymph nodes alone (one side)	42	40.00 of 105
Submaxillary and external jugular lymph nodes (one side)	13	12.38 of 105
External jugular lymph nodes (one side)	8	7.61 of 105
Superior deep cervical lymph nodes (one side)	5	4.76 of 105
Submaxillary lymph nodes and salivary glands (one side)	3	2.85 of 105
Submaxillary, external jugular, superior and inferior deep cervical lymph nodes (one side)	3	2.85 of 105
Submaxillary lymph nodes and salivary gland, and external jugular lymph nodes (one side)	2	1.90 of 105
Submaxillary, external jugular, and superior deep cervical lymph nodes (one side)	2	1.90 of 105
Submaxillary, anterior cervical, external jugular, and superior deep cervical lymph nodes (one side)	2	1.90 of 105
Submaxillary, external jugular, and supraclavicular lymph nodes (one side)	2	1.90 of 105
Submaxillary and submental lymph nodes (one side)	2	1.90 of 105
Anterior cervical lymph nodes (one side)	2	1.90 of 105
External jugular, superior and inferior deep cervical lymph nodes (one side)	2	1.90 of 105
Submaxillary lymph nodes (both sides)	2	1.90 of 105
Submaxillary and superior deep cervical lymph nodes (one side)	1	0.95 of 105
Submaxillary, submental, anterior cervical, external jugular, superior and inferior deep cervical lymph nodes (one side)	1	0.95 of 105
Submaxillary lymph nodes and salivary gland, anterior cervical, external jugular, superior and inferior deep cervical lymph nodes (one side)	1	0.95 of 105
Submaxillary and supraclavicular lymph nodes (one side)	1	0.95 of 105
Submaxillary, anterior cervical and external jugular lymph nodes (one side)	1	0.95 of 105
Submaxillary lymph nodes and salivary gland, external jugular, anterior cervical, and superior deep cervical lymph nodes (one side)	1	0.95 of 105
Submaxillary lymph nodes and salivary gland, external jugular, superior and inferior deep cervical lymph nodes (one side)	1	0.95 of 105
Anterior cervical and external jugular lymph nodes (one side)	1	0.95 of 105
Anterior cervical, external jugular, and superior deep cervical lymph nodes (one side)	1	0.95 of 105

PATHOLOGIC FINDINGS IN CASES IN WHICH LYMPH NODES AND SALIVARY GLANDS WERE REMOVED—*Continued*

	Cases	Per Cent.
Anterior cervical and submental lymph nodes (one side)	1	0.95 of 105
Superior and inferior deep cervical lymph nodes (one side)	1	0.95 of 105
Parotid lymph nodes (one side)	1	0.95 of 105
Parotid lymph nodes and salivary gland and superior and inferior deep cervical lymph nodes (one side)	1	0.95 of 105
Parotid and superior deep cervical lymph nodes (one side)	1	0.95 of 105
Left submaxillary and external jugular lymph nodes and right external jugular lymph nodes	1	0.95 of 105

TOTAL INVOLVEMENT (FIG. 12)

			Cases	Per Cent.
Submaxillary lymph nodes			81	77.14 of 105
Cervical lymph nodes (one or more groups)			54	51.42 of 105
Anterior cervical lymph nodes	11	20.37% of 54 or		10.47 of 105
External jugular lymph nodes	42	77.77% of 54 or		40.00 of 105
Superior deep cervical lymph nodes	23	42.59% of 54 or		21.90 of 105
Inferior deep cervical lymph nodes	10	18.51% of 54 or		9.52 of 105
Submaxillary salivary glands			8	7.61 of 105
Submental lymph nodes			4	3.80 of 106
Parotid lymph nodes			3	2.85 of 105
Supraclavicular lymph nodes			3	2.85 of 105
Parotid salivary gland			1	0.95 of 105
Submaxillary lymph nodes (both sides)			2	1.90 of 105
External jugular lymph nodes (both sides)			1	0.95 of 105
Sternocleidomastoid			22	20.95 of 105

CONDITION INOPERABLE

	Cases	Per Cent.
Group 1	13	12.87 of 101
Group 2	40	39.60 of 101
Group 3	6	5.94 of 101
Group 4	8	7.92 of 101
Group 5	4	3.96 of 101
Group 6	12	11.88 of 101
Group 7	14	13.86 of 101
Group 8	4	3.96 of 101

	Cases	Per Cent.
With inoperable epithelioma	101	27.90 of 362
With inoperable epithelioma concerning whom information has been received (all dead)	62	61.38 of 101
Refused operation after diagnosis had been made; dead, cause not stated	1	25.00 of 4

GENERAL ULTIMATE RESULTS (ALL GROUPS)

		Cases	Per Cent.
Information received		205	79.76 of 257
Living		40	19.51 of 205
Good result		39	97.50 of 40
Longest duration	17.48 years		
Shortest duration	1.5 years		
Average duration	9.16 years		
Fair result		1	2.50 of 40
Longest duration	10.63 years		
Dead		165	80.48 of 205
Good result		6	4.37 of 137
Longest duration	8.55 years		
Shortest duration	4.81 years		
Average duration	5.78 years		
Poor result		131	95.62 of 137
Longest duration	9.75 years		
Shortest duration	0.042 years		
Average duration	1.078 years		

CAUSE OF DEATH OF PATIENTS WHO RECOVERED FROM THE EPITHELIOMA (DATA FROM RELATIVE OR HOME PHYSICIAN)

	Cases	Per Cent.
Known cause	6	100.00 of 6
General disability	2	33.33 of 6
Diseases of the kidney	2	33.33 of 6
Blood poisoning	1	16.66 of 6
Cancer of the stomach	1	16.66 of 6

CAUSE OF DEATH OF PATIENTS WHO DIED IN THE CLINIC FOLLOWING OPERATION

	Cases	Per Cent.
Pneumonia (from two to nineteen days after operation)	6	50.00 of 12
Pneumonia (one month and eighteen days after operation)	1	8.33 of 12
Cerebral embolism (one day after operation)	1	8.33 of 12
Pulmonary thrombosis (six days after operation)	1	8.33 of 12
Miscellaneous (infection, secondary hemorrhage, etc. eleven to eighteen days after operation)	3	25.00 of 12
Total	12	4.66 of 257
Actual operative mortality	11	4.28 of 257

CAUSE OF DEATH OF ALL PATIENTS OPERATED ON (DATA FROM HOME PHYSICIAN, RELATIVE, OR PATHOLOGIC RECORDS OF THE CLINIC)

	Cases	Per Cent.
Known cause	149	90.30 of 165
Epithelioma	131	87.91 of 149
Pneumonia	7	4.69 of 149
General disability	2	1.34 of 149
Infection and hemorrhage	2	1.34 of 149
Diseases of the kidney	2	1.34 of 149
Blood poisoning	1	0.67 of 149
Cancer of the stomach	1	0.67 of 149
Cerebral embolism	1	0.67 of 149
Pulmonary thrombosis	1	0.67 of 149
Secondary hemorrhage	1	0.67 of 149
Unknown	16	9.69 of 165
Longest duration	8.55 years	
Shortest duration	0.002 years	
Average duration	1.50 years	

ONE HUNDRED AND FIVE CASES IN WHICH OPERATION WAS PERFORMED AND METASTASIS DEMONSTRATED

	Cases	Per Cent.
Group 1	38	36.19 of 105
Group 2	43	40.95 of 105
Group 3	5	4.76 of 105
Group 4	4	3.80 of 105
Group 5	5	4.76 of 105
Group 7	5	4.76 of 105
Group 8	5	4.76 of 105

OPERATION; NO METASTASIS DEMONSTRATED

	Cases	Per Cent.
Group 1	19	28.78 of 66
Group 2	39	59.09 of 66
Group 3	2	3.03 of 66
Group 4	2	3.03 of 66
Group 7	4	6.06 of 66

OPERATION; LYMPH NODES AND SALIVARY GLANDS NOT REMOVED

	Cases	Per Cent.
Group 1	6	6.97 of 86
Group 2	48	55.81 of 86
Group 3	4	4.65 of 86
Group 4	3	3.48 of 86
Group 5	15	17.44 of 86
Group 7	9	10.46 of 86
Group 8	1	1.16 of 86

PATIENTS WHO REFUSED TO HAVE AN OPERATION

	Cases	Per Cent.
Group 1	2	50.00 of 4
Group 2	1	25.00 of 4
Group 5	1	25.00 of 4

GENERAL ULTIMATE RESULTS—GROUP 1

METASTASIS, REGIONAL LYMPH NODES AND SALIVARY GLANDS REMOVED

	Grade 2	Grade 3	Cases	Per Cent.
No information			4	10.52 of 38
Information			34	89.47 of 38
Dead			34	100 of 34
Poor result	10 (41.66% of 24)	14 (58.33% of 24)		
Postoperative death	2	3		
Cause unknown	2	3		
Total poor result			24	100 of 24
Cause of Death				
Epithelioma			24	82.75 of 29
Pneumonia			3	10.34 of 29
Pulmonary thrombosis			1	3.44 of 29
Secondary hemorrhage			1	3.44 of 29

PATIENTS WITHOUT METASTASIS OPERATED ON, AND REGIONAL LYMPH NODES AND SALIVARY GLANDS REMOVED

	Grade 1	Grade 2	Grade 3	Cases	Per Cent.
No information				3	15.78 of 19
Information				16	84.21 of 19
Living				5	31.25 of 16
Good result		4 (80.00% of 5)	1 (20.00% of 5)		
Dead				11	68.75 of 16
Good result		2 (100.00% of 2)			
Poor result	1 (14.27% of 7)	4 (57.14% of 7)	2 (28.57% of 7)		
Postoperative death		1	1		
Total good result				7	50.00 of 14
Total poor result				7	50.00 of 14

PATIENTS WITHOUT METASTASIS OPERATED ON, AND REGIONAL LYMPH NODES AND SALIVARY GLANDS REMOVED—*Continued*

Cause of Death

	Cases	Per Cent.
Epithelioma	7	63.63 of 11
Cancer of the stomach	1	9.09 of 11
Hemorrhage and infection	1	9.09 of 11
Disease of the kidneys	1	9.09 of 11
Pneumonia	1	9.09 of 11

OPERATION PERFORMED, BUT REGIONAL LYMPH NODES AND SALIVARY GLANDS NOT REMOVED

	Grade 2	Grade 3	Grade 4	Cases	Per Cent.
Information received				6	100 of 6
Living				2	33.33 of 6
Good result	2 (100.00% of 2)				
Dead				4	66.66 of 6
Poor result	2 (50.00% of 4)	1 (25.00% of 4)	1 (25.00% of 4)		
Total good result				2	33.33 of 6
Total poor result				4	66.66 of 6

Cause of Death

Epithelioma				4	100 of 4
	Grade 1	Grade 2	Grade 3	Grade 4	
Patients with metastasis	.....	16 (42.10% of 38)	22 (57.89% of 38)		
Patients without metastasis	1 (5.20% of 19)	12 (63.15% of 19)	5 (26.31% of 19)	1 (5.26% of 19)	
Patients from whom lymph nodes and salivary glands were not removed at operation	.....	4 (66.66% of 6)	1 (16.66% of 6)	1 (16.66% of 6)	

DURATION OF LESION AT THE TIME OF PATIENT'S EXAMINATION AT THE CLINIC

	Longest	Shortest	Average
Patients with metastasis	4 years	0.083 years	0.795 years
Patients without metastasis	15 years	0.083 years	1.48 years
Patients from whom lymph nodes and salivary glands were not removed at operation	1 year	0.125 years	0.69 years

SIZE OF THE LESION AT THE TIME OF THE PATIENT'S EXAMINATION AT THE CLINIC

	Largest	Smallest	Average
Patients with metastasis	5 cm.	1 cm.	3.02 cm.
Patients without metastasis	7.5 cm.	1 cm.	2.45 cm.
Patients from whom lymph nodes and salivary glands were not removed at operation	5.0 cm.	0.7 cm.	2.3 cm.

DURATION OF POSTOPERATIVE LIFE OF PATIENTS WITH METASTASIS

	Grade 2	Grade 3	Cases	Per Cent.
No information			4	10.52 of 38
Information			34	89.47 of 38
Dead			34	100 of 34
Poor result	10 (41.66% of 24)	14 (58.33% of 24)		
Postoperative death	2	3		
Cause unknown	2	3		
			All Grades	
Longest	6.6 years	2.5 years	6.6 years	
Shortest	0.083 years	0.083 years	0.083 years	
Average	1.77 years	0.51 years	0.90 years	

DURATION OF POSTOPERATIVE LIFE OF PATIENTS WITHOUT METASTASIS

	Grade 1	Grade 2	Grade 3	Cases	Per Cent.
No information				3	15.78 of 19
Information				16	84.21 of 19
Living				5	31.25 of 16
Good result	.....	4 (80.00% of 5)	1 (20.00% of 5)		
				All Grades	
Longest	.....	9.71 years	9.78 years	9.78 years	
Shortest	.....	7.01 years	.....	7.01 years	
Average	.....	8.68 years	.....	8.9 years	
				Cases	Per Cent.
Dead				11	68.75 of 16
Good result	.....	2 (100.00% of 2)			
				All Grades	
Longest	.....	8.56 years	.....	8.56 years	
Shortest	.....	5.58 years	.....	5.58 years	
Average	.....	7.07 years	.....	7.07 years	
Poor result	1 (14.27% of 7)	4 (57.14% of 7)	2 (28.58% of 7)		
Postoperative death	.....	1	1		
Longest	9.75 years	2.18 years	3.37 years	9.75 years	
Shortest	.....	0.158 years	0.358 years	0.158 years	
Average	.....	0.89 years	1.87 years	2.43 years	

DURATION OF POSTOPERATIVE LIFE OF PATIENTS FROM WHOM REGIONAL LYMPH NODES AND SALIVARY GLANDS WERE NOT REMOVED

	Grade 2	Grade 3	Grade 4	Cases	Per Cent.
Information				6	100.00 of 6
Living				2	33.33 of 6
Good result	2 (100.00% of 2)				
Longest	8.4 years				
Shortest	7.22 years				
Average	7.81 years				
Dead				4	66.66 of 6
Poor result	2 (50.00% of 4)	1 (25.00% of 4)	1 (25.00% of 4)	All Grades	
Longest	1.16 years	0.50 years	0.71 years	1.16 years	
Shortest	0.50 years	.....	.....	0.50 years	
Average	0.83 years	.....	.....	0.718 years	

GENERAL ULTIMATE RESULTS—GROUP 2

PATIENTS WITH METASTASIS OPERATED ON WITH REMOVAL OF REGIONAL LYMPH NODES AND SALIVARY GLANDS

	Grade 2	Grade 3	Grade 4	Cases	Per Cent.
No information				9	20.93 of 43
Information				34	79.06 of 43
Living				2	5.88 of 34
Good result	2 (100.00% of 2)				
Dead				32	94.11 of 34
Poor result	10 (37.03% of 27)	15 (55.55% of 27)	2 (7.04% of 27)		
Postoperative death		1			
Cause unknown	1	3			
Total good result				2	6.89 of 29
Total poor result				27	93.10 of 29
Cause of Death					
Epithelioma				27	96.42 of 28
Infection and hemorrhage				1	3.56 of 28

PATIENTS WITHOUT METASTASIS OPERATED ON AND REGIONAL LYMPH NODES AND SALIVARY GLANDS REMOVED

	Grade 1	Grade 2	Grade 3	Cases	Per Cent.
No information				10	25.64 of 39
Information				29	74.35 of 39
Living				15	51.72 of 29
Good result	2 (14.28% of 14)	9 (64.28% of 14)	3 (21.42% of 14)		
Fair result		1 (100.00% of 1)			
Dead				14	48.27 of 29
Good result	1 (33.33% of 3)	2 (66.66% of 3)			
Poor result		5 (62.50% of 8)	3 (37.50% of 8)		
Cause unknown		3			
Total good result				17	65.38 of 26
Total fair result				1	3.84 of 26
Total poor result				8	30.76 of 26

PATIENTS OPERATED ON AND REGIONAL LYMPH NODES AND SALIVARY GLANDS NOT REMOVED

	Grade 1	Grade 2	Grade 3	Grade 4	Cases	Per Cent.
No information					14	29.16 of 48
Information					34	70.83 of 48
Living					6	17.64 of 34
Good result	3 (50.00% of 6)	3 (50.00% of 6)				
Dead					28	82.35 of 34
Poor result	2 (7.69% of 26)	16 (61.53% of 26)	7 (26.92% of 26)	1 (3.84% of 26)		
Cause unknown	1	1				
Total good result					6	18.75 of 32
Total poor result					26	81.25 of 32
	Grade 1	Grade 2	Grade 3	Grade 4		
Patients with metastasis	.....	18 (41.86% of 43)	23 (53.48% of 43)	2 (4.65% of 43)		
Patients without metastasis	5 (12.82% of 39)	27 (69.23% of 39)	7 (17.94% of 39)			
Patients from whom lymph nodes and salivary glands were not removed at operation	8 (16.66% of 48)	29 (60.41% of 48)	10 (20.83% of 48)	1 (2.08% of 48)		

DURATION OF LESION AT THE TIME OF PATIENT'S EXAMINATION AT THE CLINIC

	Longest	Shortest	Average
Patients with metastasis	7 years	0.083 years	1.045 years
Patients without metastasis	10 years	0.041 years	1.55 years
Patients from whom lymph nodes and salivary glands were not removed at operation	6 years	0.041 years	1.24 years

SIZE OF LESION AT THE TIME OF PATIENT'S EXAMINATION AT THE CLINIC

	Largest	Smallest	Average
Patients with metastasis	10 cm.	1.5 cm.	4.29 cm.
Patients without metastasis	10 cm.	1.0 cm.	3.74 cm.
Patients from whom lymph nodes and salivary glands were not removed at operation	7.5 cm.	1.5 cm.	4.43 cm.

DURATION OF POSTOPERATIVE LIFE OF PATIENTS WITH METASTASIS

	Grade 2	Grade 3	Grade 4	Cases	Per Cent.
No information				9	20.93 of 43
Information				34	79.06 of 43
Living				2	5.88 of 34
Good result	2 (100.00% of 2)				
Longest	11.12 years				
Shortest	7.10 years				
Average	9.11 years				
Dead				32	94.11 of 34
Poor result	10 (37.03% of 27)	15 (55.55% of 27)	2 (7.04% of 27)		
Postoperative death	.....	1			
Cause unknown	1	3			

	Grade 2	Grade 3	Grade 4	All Grades
Longest	5 years	1.75 years	0.45 years	5 years
Shortest	0.25 years	0.10 years	0.25 years	0.10 years
Average	0.989 years	0.61 years	0.35 years	0.74 years

DURATION OF POSTOPERATIVE LIFE OF PATIENTS WITHOUT METASTASIS

	Grade 1	Grade 2	Grade 3	Cases	Per Cent.
No information				10	25.64 of 39
Information				29	74.35 of 39
Living				15	51.72 of 29
Good result	2 (14.28% of 14)	9 (64.28% of 14)	3 (21.42% of 14)		

	Grade 1	Grade 2	Grade 3	All Grades
Longest	17.48 years	12.27 years	12.35 years	17.48 years
Shortest	7.69 years	7.25 years	10.67 years	7.25 years
Average	12.59 years	9.56 years	11.43 years	10.39 years
Fair result	.....	1 (100.00% of 1)		
Longest	.....	10.63 years		

	Cases	Per Cent.
Dead	14	48.27 of 29

	Grade 1	Grade 2	Grade 3	All Grades
Good result	1 (33.33% of 3)	2 (66.66% of 3)		
Longest	4.50 years	5.56 years	.....	5.56 years
Shortest	.....	4.30 years	.....	4.30 years
Average	.....	4.93 years	.....	4.80 years
Poor result	.....	5 (62.50% of 8)	3 (37.50% of 8)	
Cause unknown	.....	3		
Longest		4.85 years	5.04 years	5.04 years
Shortest		0.383 years	0.375 years	0.375 years
Average		1.61 years	2.29 years	1.86 years

DURATION OF POSTOPERATIVE LIFE OF PATIENTS FROM WHOM REGIONAL LYMPH NODES AND SALIVARY GLANDS WERE NOT REMOVED

	Cases	Per Cent.
No information	14	29.16 of 48
Information	34	70.83 of 48

	Grade 1	Grade 2	Grade 3	Grade 4	Cases	Per Cent.
Living					6	17.64 of 34
Good result	3 (50.00% of 6)	3 (50.00% of 6)				

	Grade 1	Grade 2	Grade 3	Grade 4	All Grades
Longest	9.10 years	9.98 years	.....	.....	9.98 years
Shortest	5.79 years	8.46 years	.....	.....	5.79 years
Average	7.33 years	8.99 years	.....	.....	8.15 years

	Cases	Per Cent.
Dead	28	82.35 of 34

	Grade 1	Grade 2	Grade 3	Grade 4	All Grades
Poor result	2 (7.69% of 26)	16 (61.53% of 26)	7 (26.92% of 26)	1 (3.84% of 26)	
Cause unknown	1	1			
Longest	5.49 years	6.90 years	0.50 years	0.083 years	6.90 years
Shortest	4.00 years	0.166 years	0.10 years	.....	0.083 years
Average	4.75 years	1.13 years	0.32 years	.....	1.15 years

GENERAL ULTIMATE RESULTS—GROUP 3

Patients With Metastasis

	Cases	Per Cent.
No information	1	20.00 of 5
Information	4	80.00 of 5

	Grade 3	Grade 4		
Dead			4	100.00 of 4
Poor result	2 (50.00% of 4)	2 (50.00% of 4)		
Total poor result			4	100.00 of 4

Patients Without Metastasis

	Cases	Per Cent.
Information	2	100.00 of 2

	Grade 4		
Dead		2	100.00 of 2
Poor result	2 (100.00% of 2)		
Total poor result		2	100.00 of 2

Patients From Whom Regional Lymph Nodes and Salivary Glands Were Not Removed at Operation

	Cases	Per Cent.
No information	2	50.00 of 4
Information	2	50.00 of 4

	Grade 3	Grade 4		
Dead			2	100.00 of 2
Poor result	1 (50.00% of 2)	1 (50.00% of 2)		
Total poor result			2	100.00 of 2
Patients with metastasis	2 (40.00% of 5)	3 (60.00% of 5)		
Patients without metastasis		2 (100.00% of 2)		
Patients from whom lymph nodes and salivary glands were not removed at operation	2 (50.00% of 4)	2 (50.00% of 4)		

Duration of Lesion at the Time of Patient's Examination at the Clinic

	Longest	Shortest	Average
Patients with metastasis	3 years	0.125 years	1.45 years
Patients without metastasis	0.5 years	0.166 years	0.33 years
Patients from whom lymph nodes and salivary glands were not removed at operation	1 year	0.33 years	0.77 years

Size of Lesion at the Time of Patient's Examination at the Clinic

	Largest	Smallest	Average
Patients with metastasis	3.7 cm.	2.5 cm.	3.1 cm.
Patients without metastasis	6.0 cm.	3.7 cm.	4.85 cm.
Patients from whom lymph nodes and salivary glands were not removed at operation	2.5 cm.	1.5 cm.	1.75 cm.

Duration of Postoperative Life of Patients With Metastasis

	Cases	Per Cent.
No information	1	20.00 of 5
Information	4	80.00 of 5

	Grade 3	Grade 4		
Dead			4	100.00 of 4
Poor result	2 (50.00% of 4)	2 (50.00% of 4)		
			All Grades	
Longest	0.25 years	0.41 years	0.41 years	
Shortest	0.05 years	0.166 years	0.05 years	
Average	0.15 years	0.29 years	0.22 years	

Duration of Postoperative Life of Patients Without Metastasis

	Cases	Per Cent.
Information	2	100.00 of 2

	Grade 4		
Dead		2	100.00 of 2
Poor result	2 (100.00% of 2)		
Longest	2.16 years		
Shortest	0.75 years		
Average	1.46 years		

Duration of Postoperative Life of Patients From Whom Regional Lymph Nodes and Salivary Glands Were Not Removed at Operation

	Cases	Per Cent.
No information	2	50.00 of 4
Information	2	50.00 of 4

	Grade 3	Grade 4		
Dead			2	100.00 of 2
Poor result	1 (50.00% of 2)	1 (50.00% of 2)		
			All Grades	
Longest	6.16 years	1.91 years	6.16 years	
Shortest			1.91 years	
Average			4.04 years	

GENERAL ULTIMATE RESULTS—GROUP 4

Patients With Metastasis

	Grade 2	Grade 3	Grade 4	Cases	Per Cent.
Information				4	100.00 of 4
Dead				4	100.00 of 4
Poor result	1 (33.33% of 3)	1 (33.33% of 3)	1 (33.33% of 3)		
Cause unknown		1			
Total poor result				3	100.00 of 3

Patients Without Metastasis

	Grade 2	Grade 3	Cases	Per Cent.
Information			2	100.00 of 2
Dead			2	100.00 of 2
Poor result	1 (100.00% of 1)			
Cause unknown		1		
Total poor result			1	100.00 of 1

Patients From Whom Regional Lymph Nodes and Salivary Glands Were Not Removed at Operation

	Grade 2	Grade 3	Cases	Per Cent.
No information			1	33.33 of 3
Information			2	66.66 of 3
Living			1	50.00 of 2
Good result	1 (100.00% of 1)			
Dead			1	50.00 of 2
Poor result		1 (100.00% of 1)		
Total good result			1	50.00 of 2
Total poor result			1	50.00 of 2

	Grade 2	Grade 3	Grade 4
Patients with metastasis	1 (25.00% of 4)	2 (50.00% of 4)	1 (25.00% of 4)
Patients without metastasis	1 (50.00% of 2)	1 (50.00% of 2)	
Patients from whom lymph nodes and salivary glands were not removed at operation	1 (33.33% of 3	1 (33.33% of 3)	1 (33.33% of 3)

Duration of Lesion at the Time of Patient's Examination at the Clinic

	Longest	Shortest	Average
Patients with metastasis	0.583 years	0.25 years	0.375 years
Patients without metastasis	0.833 years	0.583 years	0.7 years
Patients from whom lymph nodes and salivary glands were not removed at operation	1.5 years		

Size of Lesion at the Time of Patient's Examination at the Clinic

	Largest	Smallest	Average
Patients with metastasis	6.0 cm.	2 cm.	4 cm.
Patients from whom lymph nodes and salivary glands were not removed at operation	2.0 cm.		

Duration of Postoperative Life of Patients With Metastasis

	Grade 2	Grade 3	Grade 4	Cases	Per Cent.
Information				4	100.00 of 4
Dead				4	100.00 of 4
Poor result	1 (33.33% of 3)	1 (33.33% of 3)	1 (33.33% of 3)		

	Grade 2	Grade 3	All Grades
Longest	0.042 years	0.16 years	0.16 years
Shortest			0.042 years
Average			0.10 years

Duration of Postoperative Life of Patients Without Metastasis

	Grade 2	Cases	Per Cent.
Information		2	100.00 of 2
Dead		2	100.00 of 2
Poor result	1 (100.00% of 1)		
Longest	0.5 years		

Duration of Postoperative Life of Patients From Whom Regional Lymph Nodes and Salivary Glands Were Not Removed at Operation

	Grade 2	Grade 3	Cases	Per Cent.
No information			1	33.33 of 3
Information			2	66.66 of 3
Living			1	50.00 of 2
Good result	1 (100.00% of 1)			
Longest	11.15 years			
Dead			1	50.00 of 2
Poor result		1 (100.00% of 1)		
Longest		6.02 years		

GENERAL ULTIMATE RESULTS—GROUP 5

Patients With Metastasis

	Grade 2	Grade 3	Cases	Per Cent.
Information			5	100.00 of 5
Living			1	20.00 of 5
Good result	1 (100.00% of 1)			
Dead			4	80.00 of 5
Poor result	2 (66.66% of 3)	1 (33.33% of 3)		
Postoperative death		1		
Total good result			1	25.00 of 4
Total poor result			3	75.00 of 4

Cause of Death

Epithelioma	3	75.00 of 4
Cerebral embolism	1	25.00 of 4

Patients From Whom Regional Lymph Nodes and Salivary Glands Were Not Removed at Operation

	Grade 1	Grade 2	Grade 3	Grade 4	Cases	Per Cent.
No information					1	6.66 or 15
Information					14	93.33 of 15
Living					6	42.85 of 14
Good result	1 (16.66% of 6)	3 (50.00% of 6)	1 (16.66% of 6)	1 (16.66% of 6)		
Dead					8	57.14 of 14
Poor result		2 (40.00% of 5)	3 (60.00% of 5)			
Postoperative death		1	2			
Total good result					6	54.54 of 11
Total poor result					5	45.45 of 11

Cause of Death

Epithelioma	5	62.50 of 8
Pneumonia	3	37.50 of 8

	Grade 1	Grade 2	Grade 3	Grade 4
Patients with metastasis		3 (60.00% of 5)	2 (40.00% of 5)	
Patients from whom lymph nodes and salivary glands were not removed at operation	1 (6.66% of 15)	7 (46.66% of 15)	6 (40.00% of 15)	1(6.66% of 15)

Duration of Lesion at the Time of Patient's Examination at the Clinic

	Longest	Shortest	Average
Patients with metastasis	3 years	0.416 years	1.48 years
Patients from whom lymph nodes and salivary glands were not removed at operation	2 years	0.12 years	1.1 years

Size of Lesion at the Time of Patient's Examination at the Clinic

	Largest	Smallest	Average
Patients with metastasis	7.5 cm.	2 cm.	4.5 cm.
Patients from whom lymph nodes and salivary glands were not removed at operation	6.0 cm.	1 cm.	2.88 cm.

Duration of Postoperative Life of Patients With Metastasis

	Grade 2	Grade 3	Cases	Per Cent.
Information			5	100.00 of 5
Living			1	20.00 of 5
Good result	1 (100.00% of 1)			
Longest	1.5 years			
Dead			4	80.00 of 5
Poor result	2 (66.66% of 3)	1(33.33% of 3)		
			All Grades	
Longest	1.26 years	1 year	1.26 years	
Shortest	0.666 years	.....	0.666 years	
Average	0.966 years	.....	0.977 years	

Duration of Postoperative Life of Patients From Whom Regional Lymph Nodes and Salivary Glands Were Not Removed at Operation

	Grade 1	Grade 2	Grade 3	Grade 4	Cases	Per Cent.
No information					1	6.66 of 15
Information					14	93.33 of 15
Living					6	42.85 of 14
Good result	1 (16.66% of 6)	3 (50.00% of 6)	1 (16.66% of 6)	1 (16.66% of 6)		
					All Grades	
Longest	6.77 years	13.37 years	8.22 years	11.11 years	13.37 years	
Shortest	.....	7.54 years	.....	.....	6.77 years	
Average	.....	10.03 years	.....	.....	9.36 years	

DURATION OF POSTOPERATIVE LIFE OF PATIENTS FROM WHOM REGIONAL LYMPH NODES AND SALIVARY GLANDS WERE NOT REMOVED AT OPERATION—*Continued*

				Cases	Per Cent.
Dead				8	57.14 of 14
Poor result	2 (40.00% of 5)	3 (60.00% of 5)			
				All Grades	
Longest	0.275 years	0.775 years		0.775 years	
Shortest	0.083 years	0.425 years		0.083 years	
Average	0.179 years	0.6 years		0.43 years	

GENERAL ULTIMATE RESULTS—GROUP 7

PATIENTS WITH METASTASIS

	Grade 2	Grade 3	Grade 4	Cases	Per Cent.
No information				1	20.00 of 5
Information				4	80.00 of 5
Dead				4	100.00 of 4
Good result		1 (100.00% of 1)			
Poor result	1 (33.33% of 3)	1 (33.33% of 3)	1 (33.33% of 3)		
Total good result				1	25.00 of 4
Total poor result				3	75.00 of 4

Cause of Death

Epithelioma				3	75.00 of 4
General disability				1	25.00 of 4

PATIENTS WITHOUT METASTASIS

	Grade 3	Cases	Per Cent.
No information		2	50.00 of 4
Information		2	50.00 of 4
Dead		2	100.00 of 2
Poor result	2 (100.00% of 2)		
Total poor result		2	100.00 of 2

PATIENTS FROM WHOM REGIONAL LYMPH NODES AND SALIVARY GLANDS WERE NOT REMOVED AT OPERATION

	Grade 1	Grade 2	Grade 3	Grade 4	Cases	Per Cent.
No information					1	11.11 of 9
Information					8	88.88 of 9
Living					2	25.00 of 8
Good result	1 (50.00% of 2)	1 (50.00% of 2)				
Dead					6	75.00 of 8
Poor result			3 (50.00% of 6)	3 (50.00% of 6)		
Total good result					2	25.00 of 8
Total poor result					6	75.00 of 8

	Grade 1	Grade 2	Grade 3	Grade 4
Patients with metastasis		1 (20.00% of 5)	2 (40.00% of 5)	2 (40.00% of 5)
Patients without metastasis			3 (75.00% of 4)	1 (25.00% of 4)
Patients from whom lymph nodes and salivary glands were not removed at operation	1 (11.11% of 9)	2 (22.22% of 9)	3 (33.33% of 9)	3 (33.33% of 9)

DURATION OF LESION AT THE TIME OF PATIENT'S EXAMINATION AT THE CLINIC

	Longest	Shortest	Average
Patients with metastasis	3 years	0.58 years	1.2 years
Patients without metastasis	1 year	0.16 years	0.437 years
Patients from whom lymph nodes and salivary glands were not removed at operation	0.75 years	0.125 years	0.265 years

SIZE OF LESION AT THE TIME OF PATIENT'S EXAMINATION AT THE CLINIC

	Largest	Smallest	Average
Patients with metastasis	7.5 cm.	2.5 cm.	4.5 cm.
Patients without metastasis	6.0 cm.	3.0 cm.	4.5 cm.
Patients from whom lymph nodes and salivary glands were not removed at operation	3.0 cm.	1.5 cm.	2.25 cm.

DURATION OF POSTOPERATIVE LIFE OF PATIENTS WITH METASTASIS

	Grade 2	Grade 3	Grade 4	Cases	Per Cent.
No information				1	20.00 of 5
Information				4	80.00 of 5
Dead				4	100.00 of 4
Good result		1 (100.00% of 1)			
Longest		6.16 years		All Grades	
Poor result	1 (33.33% of 3)	1 (33.33% of 3)	1 (33.33% of 3)		
Longest	0.81 years	0.5 years	0.25 years	0.81 years	
Shortest				0.25 years	
Average				0.519 years	

DURATION OF POSTOPERATIVE LIFE OF PATIENTS WITHOUT METASTASIS

	Cases	Per Cent.
No information	2	50.00 of 4
Information	2	50.00 of 4

	Grade 3		
Dead		2	100.00 of 2
Poor result	2 (100.00% of 2)		
Longest	0.59 years		
Shortest	0.233 years		
Average	0.41 years		

DURATION OF POSTOPERATIVE LIFE OF PATIENTS FROM WHOM REGIONAL LYMPH NODES AND SALIVARY GLANDS WERE NOT REMOVED AT OPERATION

	Cases	Per Cent.
No information	1	11.11 of 9
Information	8	88.88 of 9

	Grade 1	Grade 2	Grade 3	Grade 4		
Living					2	25.00 of 8
Good result	1 (50.00% of 2)	1 (50.00% of 2)	.....	.....		
Longest	7.8 years	8.16 years			All Grades 8.16 years	
Shortest					7.8 years	
Average					7.98 years	

			Cases	Per Cent.
Dead			6	75.00 of 8
Poor result	3 (50.00% of 6)	3 (50.00% of 6)		
Longest	0.83 years	2.62 years	All Grades 2.62 years	
Shortest	0.306 years	0.316 years	0.316 years	
Average	0.62 years	1.23 years	0.922 years	

GENERAL ULTIMATE RESULTS—GROUP 8

PATIENTS WITH METASTASIS

	Cases	Per Cent.
No information	3	60.00 of 5
Information	2	40.00 of 5

	Grade 2	Grade 4		
Dead			2	100.00 of 2
Poor result	1 (50.00% of 2)	1 (50.00% of 2)		
Total poor result			2	100.00 of 2

PATIENTS FROM WHOM REGIONAL LYMPH NODES AND SALIVARY GLANDS WERE NOT REMOVED AT OPERATION

	Cases	Per Cent.
Information	1	100.00 of 1

	Grade 3		
Dead		1	100.00 of 1
Poor result	1 (100.00% of 1)		

	Grade 2	Grade 3	Grade 4
Patients with metastasis	1 (20.00% of 5)	2 (40.00% of 5)	2 (40.00% of 5)
Patients from whom lymph nodes and salivary glands were not removed at operation		1 (100.00% of 1)	

DURATION OF LESION AT THE TIME OF PATIENT'S EXAMINATION AT THE CLINIC

	Longest	Shortest	Average
Patients with metastasis	1.33 years	0.29 years	0.739 years
Patients from whom lymph nodes and salivary glands were not removed at operation	0.25 years		

SIZE OF LESION AT THE TIME OF PATIENT'S EXAMINATION AT THE CLINIC

	Largest
Patients from whom lymph nodes and salivary glands were not removed at operation	7.0 cm.

DURATION OF POSTOPERATIVE LIFE OF PATIENTS WITH METASTASIS

	Cases	Per Cent.
No information	3	60.00 of 5
Information	2	40.00 of 5

	Grade 2	Grade 4		
Dead			2	100.00 of 2
Poor result	1 (50.00% of 2)	1 (50.00% of 2)		
Longest	0.3 years	0.558 years	All Grades 0.558 years	
Shortest			0.3 years	
Average			0.43 years	

PATIENTS FROM WHOM REGIONAL LYMPH NODES AND SALIVARY GLANDS WERE NOT REMOVED AT OPERATION

	Cases	Per Cent.
Information	1	100.00 of 1
	Grade 3	
Dead	1	100.00 of 1
Poor result	1 (100.00% of 1)	
Longest	0.216 years	

PATIENTS WITH METASTASIS—ALL GROUPS

	Grade 2	Grade 3	Grade 4	Cases	Per Cent.
No information				18	17.14 of 105
Information				87	82.85 of 105
Living				3	3.44 of 87
Good result	3 (100.00% of 3)				
Dead				84	96.55 of 87
Good result		1 (100.00% of 1)			
Poor result	25 (37.87% of 66)	34 (51.51% of 66)	7 (10.60% of 66)		
Postoperative death	2	5			
Cause unknown	3	7			
Total good result				4	5.71 of 70
Total poor result				66	94.28 of 70

CAUSE OF DEATH

	Cases	Per Cent.
Epithelioma	66	89.18 of 74
Pneumonia	3	4.05 of 74
Cerebral embolism	1	1.35 of 74
General disability	1	1.35 of 74
Infection and hemorrhage	1	1.35 of 74
Pulmonary thrombosis	1	1.35 of 74
Secondary hemorrhage	1	1.35 of 74

Grade 2	Grade 3	Grade 4
40 (38.09% of 105)	55 (52.38% of 105)	10 (9.52% of 105)

DURATION OF LESION AT THE TIME OF PATIENT'S EXAMINATION AT THE CLINIC

Longest	Shortest	Average
7 years	0.083 years	0.966 years

SIZE OF LESION AT THE TIME OF PATIENT'S EXAMINATION AT THE CLINIC

Largest	Smallest	Average
10.0 cm.	1.0 cm.	3.695 cm.

DURATION OF POSTOPERATIVE LIFE

	Grade 2	Grade 3	Grade 4	Cases	Per Cent.
No information				18	17.14 of 105
Information				87	82.85 of 105
Living				3	3.44 of 87
Good result	3 (100.00% of 3)				
Longest	11.12 years				
Shortest	1.5 years				
Average	6.57 years				
Dead				84	96.55 of 87
Good result		1 (100.00% of 1)			
Longest		6.16 years			
Poor result	25 (37.87% of 66)	34 (51.51% of 66)	7 (10.60% of 66)		
Longest	6.6 years	2.5 years	0.558 years	All Grades 6.6 years	
Shortest	0.083 years	0.042 years	0.16 years	0.042 years	
Average	1.15 years	0.53 years	0.32 years	0.74 years	
Postoperative death	2	5			
Cause unknown	3	7			

PATIENTS WITHOUT METASTASIS—ALL GROUPS

	Grade 1	Grade 2	Grade 3	Grade 4	Cases	Per Cent.
No information					15	22.72 of 66
Information					51	77.27 of 66
Living					20	39.21 of 51
Good result	2 (10.53% of 19)	13 (68.42% of 19)	4 (21.05% of 19)			
Fair result		1 (100.00% of 1)				
Dead					31	60.78 of 51

PATIENTS WITHOUT METASTASIS—ALL GROUPS—*Continued*

					Cases	Per Cent.
Good result	1 (20.00% of 5)	4 (80.00% of 5)				
Poor result	1 (5.00% of 20)	10 (50.00% of 20)	7 (35.00% of 20)	2 (10.00% of 20)		
Postoperative death		1	1			
Cause unknown		3	1			
Total good result					24	53.33 of 45
Total fair result					1	2.22 of 45
Total poor result					20	44.44 of 45

Cause of Death

				Cases	Per Cent.
Epithelioma				20	90.90 of 22
Pneumonia				1	4.54 of 22
Infection and hemorrhage				1	4.54 of 22
Grade 1	Grade 2	Grade 3	Grade 4		
6 (9.09% of 66)	40 (60.60% of 66)	16 (24.24% of 66)	4 (6.06% of 66)		

Duration of Lesion at the Time of Patient's Examination at the Clinic

Longest	Shortest	Average
15 years	0.04 years	1.40 years

Size of Lesion at the Time of Patient's Examination at the Clinic

Largest	Smallest	Average
10 cm.	1 cm.	3.39 cm.

Duration of Postoperative Life

					Cases	Per Cent.
No information					15	22.72 of 66
Information					51	77.27 of 66
	Grade 1	Grade 2	Grade 3	Grade 4		
Living					20	39.21 of 51
Good result	2 (10.53% of 19)	13 (68.42% of 19)	4 (21.05% of 19)			
					All Grades	
Longest	17.48 years	12.27 years	12.35 years	.....	17.48 years	
Shortest	7.69 years	7.01 years	9.78 years	.....	7.01 years	
Average	12.59 years	9.28 years	11.01 years	.....	10.00 years	
Fair result	.....	1 (100.00% of 1)				
Longest	.....	10.63 years				
					Cases	Per Cent.
Dead					31	60.78 of 51
Good result	1 (20.00% of 5)	4 (80.00% of 5)				
					All Grades	
Longest	4.50 years	8.56 years	.....	.....	8.56 years	
Shortest	.....	4.30 years	.....	.....	4.30 years	
Average	.....	6.00 years	.....	.....	5.71 years	
Poor result	1 (5.00% of 20)	10 (50.00% of 20)	7 (35.00% of 20)	2 (10.00% of 20)		
Longest	9.75 years	4.85 years	5.04 years	2.16 years	9.75 years	
Shortest	.....	0.158 years	0.23 years	0.75 years	0.158 years	
Average	.....	1.21 years	1.63 years	1.46 years	1.80 years	
Postoperative death	.....	1	1			
Cause unknown	.....	3	1			

PATIENTS FROM WHOM REGIONAL LYMPH NODES AND SALIVARY GLANDS WERE NOT REMOVED AT OPERATION—ALL GROUPS

					Cases	Per Cent.
No information					19	22.09 of 86
Information					67	77.90 of 86
	Grade 1	Grade 2	Grade 3	Grade 4		
Living					17	25.37 of 67
Good result	5 (29.41% of 17)	10 (58.82% of 17)	1 (5.88% of 17)	1 (5.88% of 17)		
Dead					50	74.62 of 67
Poor result	2 (4.44% of 45)	20 (44.44% of 45)	17 (37.77% of 45)	6 (13.33% of 45)		
Postoperative death	.....	1	3			
Cause unknown	1	1				
Total good result					17	27.41 of 62
Total poor result					45	72.58 of 62

Cause of Death

				Cases	Per Cent.
Epithelioma				45	93.75 of 48
Pneumonia				3	6.25 of 48
Grade 1	Grade 2	Grade 3	Grade 4		
10 (11.62% of 86	43 (50.00% of 86)	24 (27.90% of 86)	9 (10.46% of 86)		

Duration of Lesion at the Time of the Patient's Examination at the Clinic

Longest	Shortest	Average
6 years	0.041 years	1.05 years

Size of Lesion at the Time of the Patient's Examination at the Clinic

Largest	Smallest	Average
7.5 cm.	0.7 cm.	3.75 cm.

DURATION OF POSTOPERATIVE LIFE

	Cases	Per Cent.
No information	19	22.09 of 86
Information	67	77.90 of 86

	Grade 1	Grade 2	Grade 3	Grade 4	
Living					17 25.37 of 67
Good result	5 (29.41% of 17)	10 (58.82% of 17)	1 (5.88% of 17)	1 (5.88% of 17)	
Longest	9.10 years	13.37 years	8.22 years	11.11 years	All Grades 13.37 years
Shortest	5.79 years	7.22 years	.....	.....	5.79 years
Average	7.31 years	9.19 years	.....	.....	8.60 years

	Cases	Per Cent.
Dead	50	74.62 of 67

	Grade 1	Grade 2	Grade 3	Grade 4	
Poor result	2 (4.44% of 45)	20 (44.44% of 45)	17 (37.77% of 45)	6 (13.33% of 45)	
Longest	5.49 years	6.90 years	6.62 years	2.625 years	All Grades 6.90 years
Shortest	4.00 years	0.083 years	0.10 years	0.083 years	0.083 years
Average	4.75 years	1.009 years	1.14 years	1.06 years	1.23 years
Postoperative death	.....	1	2		
Cause unknown	1	1			

POSTOPERATIVE RESULTS ACCORDING TO GRADE

GROUP 1

	Grade 1	Grade 2	Grade 3	Grade 4	All Grades
Information	1 (100.00% of 1)	29 (90.62% of 32)	25 (89.28% of 28)	1 (50.00% of 2)	56 (88.88% of 63)
Living	.....	6 (20.68% of 29)	1 (4.00% of 25)	.....	7 (12.50% of 56)
Good result	.....	6 (100.00% of 6)	1 (100.00% of 1)	.....	7 (15.90% of 44)
Dead	1 (100.00% of 1)	23 (79.31% of 29)	24 (96.00% of 25)	1 (100.00% of 1)	49 (87.50% of 56)
Good result	.....	2 (11.11% of 18)	.....	.....	2 (4.54% of 44)
Poor result	1 (100.00% of 1)	16 (88.88% of 18)	17 (100.00% of 17)	1 (100.00% of 1)	35 (79.54% of 44)
Total results (dead)	.....	.....	.....	.....	37 (84.09% of 44)
Postoperative death	3	4			
Cause of death not stated	2	3			
Total good result	.....	8 (33.33% of 24)	1 (5.55% of 18)	.....	9 (20.45% of 44)
Total poor result	1 (100.00% of 1)	16 (66.66% of 24)	17 (94.44% of 18)	1 (100.00% of 1)	35 (79.54% of 44)

GROUP 2

	Grade 1	Grade 2	Grade 3	Grade 4	All Grades
Information	9 (69.23% of 13)	53 (71.62% of 74)	32 (80.00% of 40)	3 (100.00% of 3)	97 (74.61% of 130)
Living	5 (55.56% of 9)	15 (28.30% of 53)	3 (9.37% of 32)	.....	23 (23.71% of 97)
Good result	5 (100.00% of 5)	14 (93.33% of 15)	3 (100.00% of 3)	.....	22 (25.28% of 87)
Fair result	.....	1 (6.66% of 15)	.....	.....	1 (1.14% of 87)
Dead	4 (44.44% of 9)	38 (71.69% of 53)	29 (90.62% of 32)	3 (100.00% of 3)	74 (76.28% of 97)
Good result	1 (33.33% of 3)	2 (6.06% of 33)	.....	.....	3 (3.44% of 87)
Poor result	2 (66.66% of 3)	31 (93.93% of 33)	25 (100.00% of 25)	3 (100.00% of 3)	61 (70.11% of 87)
Total results (dead)	.....	.....	.....	.....	64 (73.50% of 87)
Postoperative death	.....	.....	1		
Cause of death not stated	1	5	3		
Total good result	6 (75.00% of 8)	16 (33.33% of 48)	3 (10.71% of 28)	.....	25 (28.73% of 87)
Total fair result	.....	1 (2.08% of 48)	.....	.....	1 (1.14% of 87)
Total poor result	2 (25.00% of 8)	31 (64.58% of 48)	25 (89.28% of 28)	3 (100.00% of 3)	61 (70.11% of 87)

GROUP 3

	Grade 1	Grade 2	Grade 3	Grade 4	All Grades
Information	.....	.....	3 (75.00% of 4)	5 (71.42% of 7)	8 (72.72% of 11)
Dead	.....	.....	3 (100.00% of 3)	5 (100.00% of 5)	8 (100.00% of 8)
Poor result	.....	.....	3 (100.00% of 3)	5 (100.00% of 5)	8 (100.00% of 8)
Total poor result	.....	.....	3 (100.00% of 3)	5 (100.00% of 5)	8 (100.00% of 8)

POSTOPERATIVE RESULTS ACCORDING TO GRADE—*Continued*

GROUP 4

	Grade 1	Grade 2	Grade 3	Grade 4	All Grades
Information	.....	3 (100.00% of 3)	4 (100.00% of 4)	1 (50.00% of 2)	8 (88.88% of 9)
Living	.....	1 (33.33% of 3)	.....	.....	1 (12.50% of 8)
Good result	.....	1 (100.00% of 1)	.....	.....	1 (16.66% of 6)
Dead	.....	2 (66.66% of 3)	4 (100.00% of 4)	1 (100.00% of 1)	7 (87.50% of 8)
Poor result	.....	2 (100.00% of 2)	2 (50.00% of 4)	1 (100.00% of 1)	5 (83.33% of 6)
Cause of death not stated	.....	2			
Total good result	.....	1 (33.33% of 3)	.....	.....	1 (16.66% of 6)
Total poor result	.....	2 (66.66% of 3)	2 (100.00% of 2)	1 (100.00% of 1)	5 (83.33% of 6)

GROUP 5

	Grade 1	Grade 2	Grade 3	Grade 4	All Grades
Information	1 (100.00% of 1)	9 (90.00% of 10)	8 (100.00% of 8)	1 (100.00% of 1)	19 (95.00% of 20)
Living	1 (100.00% of 1)	4 (44.44% of 9)	1 (12.50% of 8)	1 (100.00% of 1)	7 (36.84% of 19)
Good result	1 (100.00% of 1)	4 (100.00% of 4)	1 (100.00% of 1)	1 (100.00% of 1)	7 (46.66% of 15)
Dead	.....	5 (55.55% of 9)	7 (87.50% of 8)	.....	12 (63.15% of 19)
Poor result	.....	4 (100.00% of 4)	4 (100.00% of 4)	.....	8 (53.33% of 15)
Postoperative death	.....	1	3		
Total good result	1 (100.00% of 1)	4 (50.00% of 8)	1 (20.00% of 5)	1 (100.00% of 1)	7 (46.66% of 15)
Total poor result	.....	4 (50.00% of 8)	4 (80.00% of 5)	.....	8 (53.33% of 15)

GROUP 7

	Grade 1	Grade 2	Grade 3	Grade 4	All Grades
Information	1 (100.00% of 1)	2 (66.66% of 3)	7 (87.50% of 8)	4 (66.66% of 6)	14 (77.77% of 18)
Living	1 (100.00% of 1)	1 (50.00% of 2)	.....	.....	2 (14.28% of 14)
Good result	1 (100.00% of 1)	1 (100.00% of 1)	.....	.....	2 (14.28% of 14)
Dead	.....	1 (50.00% of 2)	7 (100.00% of 7)	4 (100.00% of 4)	12 (85.71% of 14)
Good result	.....	.....	1 (14.28% of 7)	.....	1 (7.14% of 14)
Poor result	.....	1 (100.00% of 1)	6 (85.71% of 7)	4 (100.00% of 4)	11 (78.57% of 14)
Total results (dead)	.....	.....	.....	.....	12 (85.71% of 14)
Total good results	1 (100.00% of 1)	1 (50.00% of 2)	1 (14.28% of 7)	.....	3 (21.42% of 14)
Total poor results	.....	1 (50.00% of 2)	6 (85.71% of 7)	4 (100.00% of 4)	11 (78.57% of 14)

GROUP 8

	Grade 1	Grade 2	Grade 3	Grade 4	All Grades
Information	.....	1 (100.00% of 1)	1 (33.33% of 3)	1 (50.00% of 2)	3 (50.00% of 6)
Dead	.....	1 (100.00% of 1)	1 (100.00% of 1)	1 (100.00% of 1)	3 (100.00% of 3)
Poor result	.....	1 (100.00% of 1)	1 (100.00% of 1)	1 (100.00% of 1)	3 (100.00% of 3)
Total poor result	.....	1 (100.00% of 1)	1 (100.00% of 1)	1 (100.00% of 1)	3 (100.00% of 3)

ALL GROUPS

	Grade 1	Grade 2	Grade 3	Grade 4	All Grades
Information	12 (75.00% of 16)	97 (78.86% of 123)	80 (84.21% of 95)	16 (69.56% of 23)	205 (79.76% of 257)
Living	7 (58.33% of 12)	27 (27.83% of 97)	5 (6.25% of 80)	1 (6.25% of 16)	40 (19.51% of 205)
Good result	7 (100.00% of 7)	26 (96.29% of 27)	5 (100.00% of 5)	1 (100.00% of 1)	39 (22.03% of 177)
Fair result	.....	1 (3.70% of 27)	.....	.....	1 (0.56% of 177)
Dead	5 (41.66% of 12)	70 (72.16% of 97)	75 (93.75% of 80)	15 (93.75% of 16)	165 (80.48% of 205)
Good result	1 (25.00% of 4)	4 (6.77% of 59)	1 (1.69% of 59)	.....	6 (3.38% of 177)
Poor result	3 (75.00% of 4)	55 (93.22% of 59)	58 (98.30% of 59)	15 (100.00% of 15)	131 (74.01% of 177)
Total results (dead)	.....	.....	.....	.....	137 (77.40% of 177)

POSTOPERATIVE RESULTS ACCORDING TO GRADE—*Continued*

All Groups

	Grade 1	Grade 2	Grade 3	Grade 4	All Grades
Postoperative deaths	.....	4	8		
Cause of death not stated	1	7	8		
Total good result	8 (72.72% of 11)	30 (34.88% of 86)	6 (9.37% of 64)	1 (6.25% of 16)	45 (25.42% of 177)
Total fair result	.....	1 (1.16% of 86)	.....	.....	1 (0.56% of 177)
Total poor result	3 (27.27% of 11)	55 (63.99% of 86)	58 (90.62% of 64)	15 (93.75% of 16)	131 (74.01% of 177)

DURATION OF POSTOPERATIVE LIFE ACCORDING TO GRADE

Group 1

	Grade 1	Grade 2	Grade 3	Grade 4	All Grades
Information	.....	.....	.....	.....	44 cases
Living	.....	.....	.....	.....	7 cases
Good result	.....	6 cases	1 case		
Longest	.....	9.71 years	9.78 years	.....	9.78 years
Shortest	.....	7.01 years	.....	.....	7.01 years
Average	.....	8.39 years	.....	.....	8.59 years
Dead	.....	.....	.....	.....	37 cases
Good result	.....	2 cases			
Longest	.....	8.56 years			
Shortest	.....	5.58 years			
Average	.....	7.07 years			
Poor result	1 case	16 cases	17 cases	1 case	
Longest	9.75 years	6.68 years	3.375 years	0.71 years	
Shortest	.....	0.08 years	0.08 years		
Average	.....	1.25 years	0.67 years	.....	0.917 years
Average duration of life of all patients (living and dead) who obtained good results.					9.9 years

Group 2

	Grade 1	Grade 2	Grade 3	Grade 4	All Grades
Information	.....	.....	.....	.....	87 cases
Living	.....	.....	.....	.....	23 cases
Good result	5 cases	14 cases	3 cases		
Longest	17.48 years	12.27 years	12.35 years	.....	17.48 years
Shortest	5.79 years	7.10 years	10.67 years	.....	5.79 years
Average	9.43 years	9.47 years	11.43 years	.....	9.66 years
Fair result	.....	1 case			
Longest	.....	10.63 years			
Dead	.....	.....	.....	.....	64 cases
Good result	1 case	2 cases			
Longest	4.5 years	5.57 years	.....	.....	5.57 years
Shortest	.....	4.31 years	.....	.....	4.31 years
Average	.....	4.93 years	.....	.....	4.80 years
Poor result	2 cases	31 cases	25 cases	3 cases	
Longest	5.49 years	6.9 years	5.04 years	0.45 years	6.90 years
Shortest	4.0 years	0.1666 years	0.10 years	0.0833 years	0.083 years
Average	4.75 years	1.16 years	0.735 years	0.26 years	1.06 years
Date of death not obtained	.....	.....	1 case		
Average duration of life of all patients (living and dead) who obtained good results.					9.41 years

Group 3

	Grade 1	Grade 2	Grade 3	Grade 4	All Grades
Information	.....	.....	.....	.....	8 cases
Dead	.....	.....	.....	.....	8 cases
Poor result	.....	.....	8 cases	5 cases	
Longest	.....	.....	6.16 years	1.91 years	6.16 years
Shortest	.....	.....	0.05 years	.....	0.05 years
Average	.....	.....	2.15 years	1.08 years	1.48 years

Group 4

	Grade 1	Grade 2	Grade 3	Grade 4	All Grades
Information	.....	.....	.....	.....	6 cases
Living	.....	.....	.....	.....	1 case
Good result	.....	1 case			
Longest	.....	11.15 years	.....	.....	11.15 years
Dead	.....	.....	.....	.....	5 cases
Poor result	.....	2 cases	2 cases	1 case	
Longest	.....	0.5 years	6.62 years	0.16 years	6.62 years
Shortest	.....	.....	0.042 years	.....	0.042 years
Average	.....	.....	3.32 years	.....	1.83 years
Date of death not obtained	.....	1 case			

Group 5

	Grade 1	Grade 2	Grade 3	Grade 4	All Grades
Information	.....	.....	.....	.....	15 cases
Living	.....	.....	.....	.....	7 cases
Good result	1 case	4 cases	1 case	1 case	
Longest	6.77 years	13.37 years	8.22 years	11.116 years	13.37 years
Shortest	.....	1.5 years	.....	.....	1.5 years
Average	.....	7.80 years	.....	.....	8.24 years
Dead	.....	.....	.....	.....	8 cases
Poor result	.....	4 cases	4 cases		
Longest	.....	1.26 years	1 year	.....	1.26 years
Shortest	.....	0.083 years	0.425 years	.....	0.083 years
Average	.....	0.57 years	0.7 years	.....	0.635 years

DURATION OF POSTOPERATIVE LIFE ACCORDING TO GRADE—*Continued*

GROUP 7

	Grade 1	Grade 2	Grade 3	Grade 4	All Grades
Information					14 cases
Living					2 cases
Good result	1 case	1 case			
Longest	7.8 years	8.16 years			8.16 years
Shortest					7.8 years
Average					7.987 years
Dead					12 cases
Good result			1 case		
Longest			6.16 years		6.16 years
Poor result		1 case	6 cases	4 cases	
Longest		0.81 years	0.83 years	2.625 years	2.625 years
	of 1)	of 24)	of 18)	of 1)	of 44)
		of 24)	of 18)		of 44)
Shortest			0.233 years	0.25 years	0.233 years
Average			0.53 years		0.98 years
Average duration of life of all patients (living and dead) who obtained good results.					7.38 years

GROUP 8

	Grade 1	Grade 2	Grade 3	Grade 4	All Grades
Information					3 cases
Dead					3 cases
Poor result		1 case	1 case	1 case	
Longest		0.3 years	0.216 years	0.558 years	0.558 years
Shortest					0.216 years
Average					0.358 years

ALL GROUPS

	Grade 1	Grade 2	Grade 3	Grade 4	All Grades
Information					177 cases
Living					40 cases
Good result	7 cases	26 cases	5 cases	1 case	
Longest	17.48 years	13.37 years	12.35 years	11.116 years	17.48 years
Shortest	5.79 years	1.5 years	8.22 years		1.5 years
Average	8.82 years	7.9 years	9.62 years		9.16 years
Fair result		1 case			
Longest		10.63 years			
Dead					137 cases
Good result	1 case	4 cases	1 case		
Longest	4.5 years	8.55 years	6.16 years		8.55 years
Shortest		4.31 years			4.31 years
Average		6.00 years			5.78 years
Poor result	3 cases	55 cases	58 cases	15 cases	
Longest	9.75 years	6.9 years	6.62 years	2.625 years	9.75 years
Shortest	4.00 years	0.083 years	0.042 years	0.083 years	0.042 years
Average	6.41 years	1.11 years	0.848 years	0.77 years	1.078 years
Date of death not obtained		1 case	1 case		
Average duration of life of all patients (living and dead) who obtained good results.					8.71 years

CONCLUSIONS

1. The 362 cases considered here represent 18.1 per cent. of 2,000 cases of general epithelioma observed in the Mayo Clinic from Nov. 1, 1904 to July 22, 1915.

2. Males outnumber females about eight to one, there being 88.95 per cent. of the former and 11.05 per cent. of the latter.

3. In 9.39 per cent. of the patients, there was a family history of malignancy.

4. The average age of all patients was 54.38 years. Group 2 had the oldest average age, 56.72, and Group 3, the youngest average age, 48.23.

5. Of the males, 34.51 per cent. were farmers, which approximates the 33.85 per cent. in cases of epithelioma of the genito-urinary organs, contrasted with 56.7 per cent. of farmers among the patients with squamous-cell epithelioma of the lip, and 53.96 per cent. among patients with squamous-cell epithelioma of the skin.

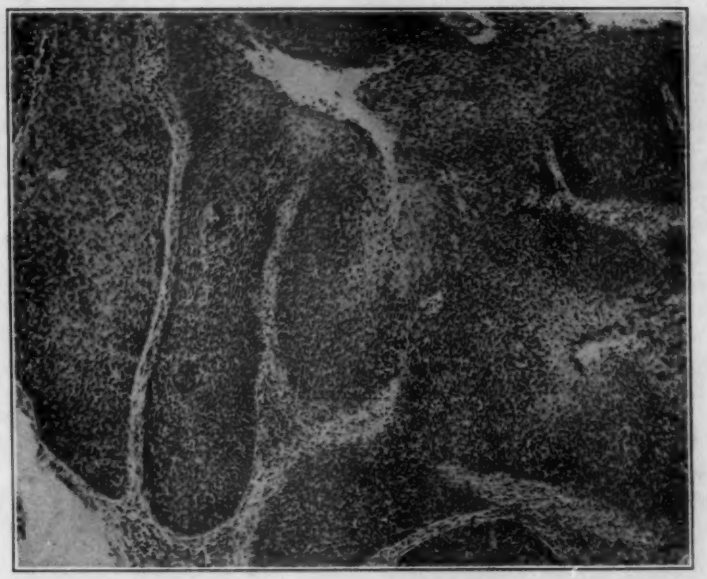

Fig. 8.—Grade 3 epithelioma of the tonsil, similar to that shown in Figure 7.

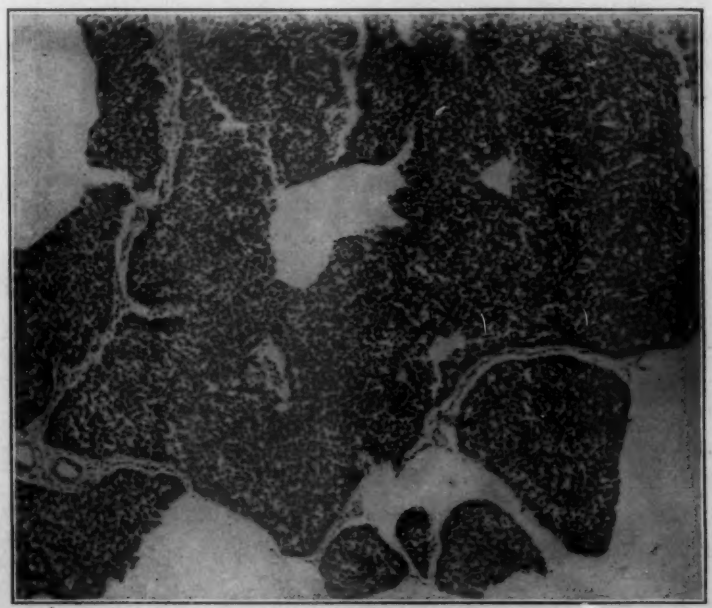

Fig. 9.—Grade 4 epithelioma of the floor of the mouth. There is no differentiation. The growth was highly malignant.

6. A definite history of syphilis, or a positive Wassermann reaction, or both, was obtained in twenty-five (12.5 per cent.) of 200 cases in which such data were available, and representing all groups; while the same findings were obtained in seventeen (31.49 per cent.) of fifty-four cases of epithelioma of the tongue.

7. In 33.14 per cent. of the patients, there was a previous crack, leukoplakia, ulcer or wart at the site of the cancer.

8. Bad teeth were noted in 20.16 per cent. of the patients.

9. Group 2 represents 47.23 per cent. of the lesions; Group 1, 21.54 per cent., and the remaining six groups range from 8.83 to 2.76 per cent.

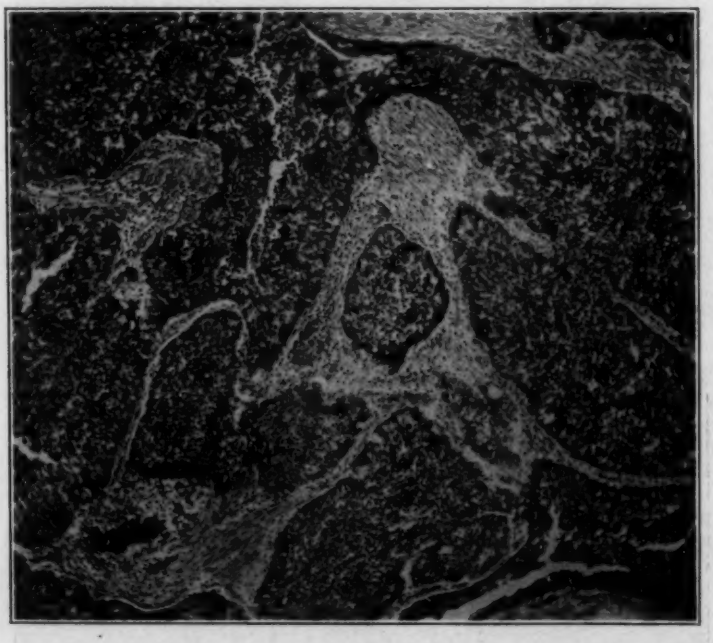

Fig. 10.—Grade 4 epithelioma of the tongue, similar to that shown in Figure 9.

10. The average duration of the lesion in all the cases was 1.18 years. Group 6 had the longest average duration, 2.35 years, and Group 7, the shortest, 0.587 years.

11. The average size of the lesion in all cases was 3.6 cm. Group 2 had the largest average size, 4.14 cm., and Group 1, the smallest, 2.83.

12. Operation was performed in 70.99 per cent. of all patients; 27.9 per cent. presented inoperable conditions, and 1.1 per cent. refused operation after the diagnosis had been made.

13. In a classification of all the epitheliomas of cavities and internal organs of the head and neck according to cellular activity, 4.41 per

cent. were graded 1; 44.47 per cent., 2; 40.05 per cent., 3; and 11.04 per cent., 4. If the groups are considered individually, Group 2 has the highest percentage of lesions of Grade 1 and 2 (7.6 per cent. of the former and 54.38 per cent. of the latter); while Group 6 has the highest percentage of Grade 3 lesions (83.33 per cent.), and Group 3 has the highest percentage for Grade 4 lesions (58.82 per cent.).

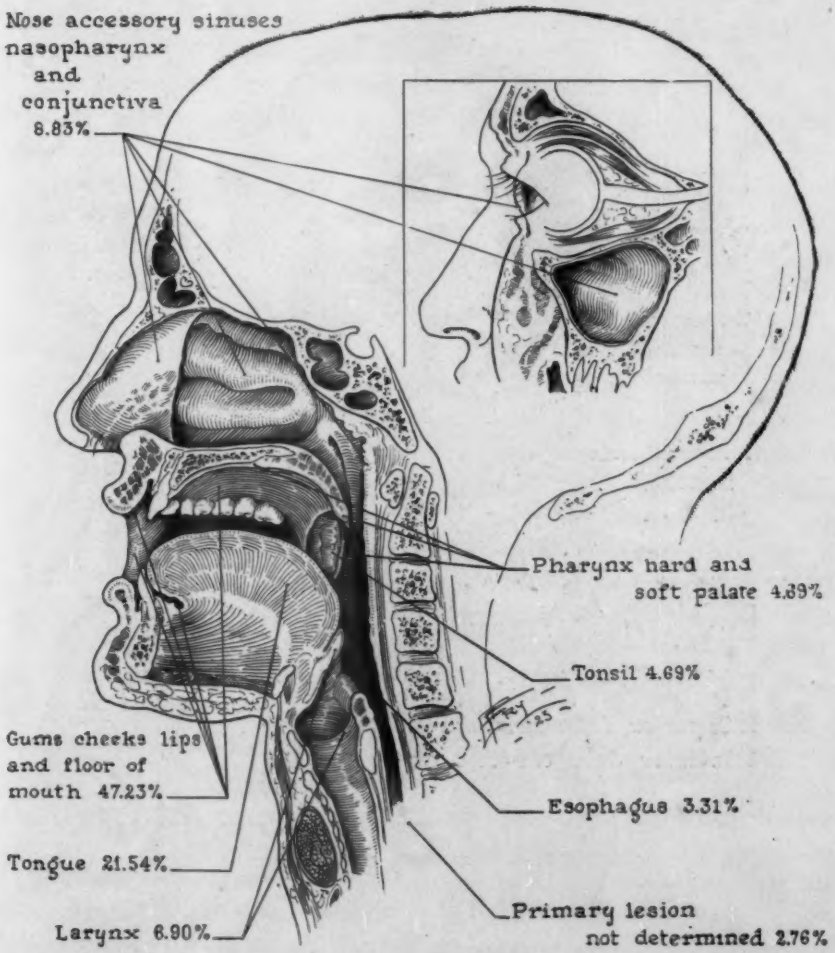
Nose accessory sinuses nasopharynx and conjunctiva 8.83%
Pharynx hard and soft palate 4.89%
Tonsil 4.69%
Gums cheeks lips and floor of mouth 47.23%
Esophagus 3.31%
Tongue 21.54%
Primary lesion not determined 2.76%
Larynx 6.90%

Fig. 11.—Percentages of points of origin of epithelioma.

14. Of the 257 patients operated on, 66.53 per cent. had one or more groups of the regional lymph nodes or salivary glands removed, of which metastasis was demonstrated in 61.4 per cent.

15. The submaxillary lymph nodes were involved more often than any others (77.14 per cent.); the cervical lymph nodes were involved in

51.42 per cent., and the sternocleidomastoid was involved in 20.95 per cent.

16. Of the patients operated on, 79.76 per cent. have been traced; 19.51 per cent. are living, and 80.48 per cent. are dead.

17. Of the living patients, 97.50 per cent. report good results. They have lived on an average of 9.16 years since the last or only operation.

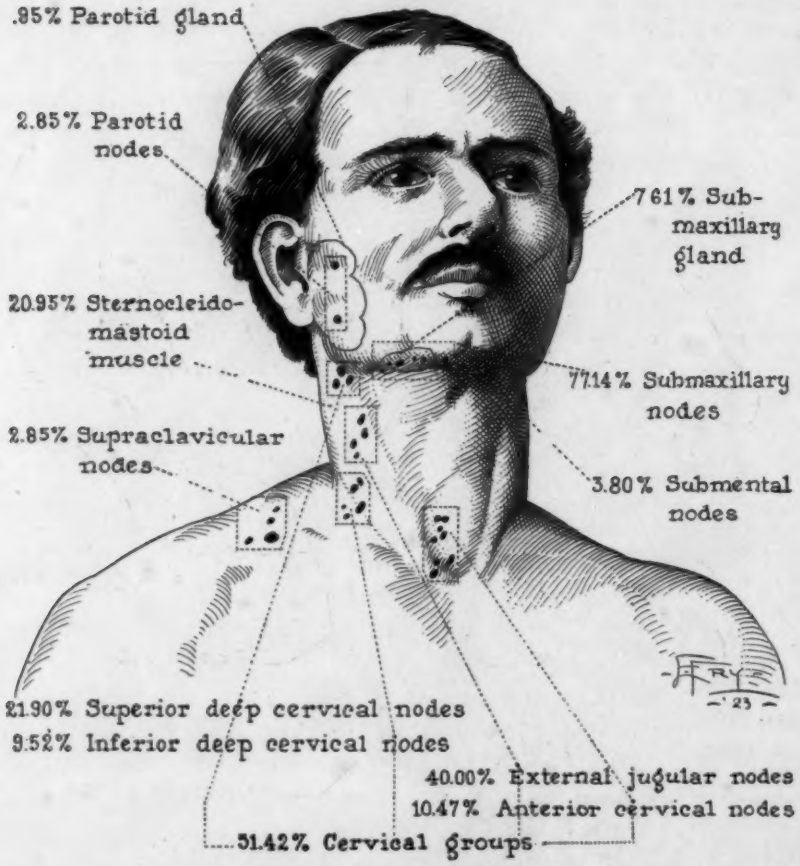

Fig. 12.—Percentages of location of metastasis.

18. Excluding immediate postoperative deaths, and deaths in which the cause was not determined, 4.37 per cent. of the patients obtained good results and lived on an average of 5.78 years after the last or only operation.

19. Excluding postoperative deaths and deaths in which the cause was not determined, 95.62 per cent. of the deaths were caused by epithelioma. These patients lived on an average of 1.078 years after the last or only operation.

20. Of the patients with metastasis operated on, 6.89 per cent. in Group 2, 25 per cent. in Group 5 and 25 per cent. in Group 7 obtained good results; while 100 per cent. of the patients with metastasis in Group 1, 93.1 per cent. in Group 2, 100 per cent. in Group 3, 100 per cent. in Group 4, 75 per cent. in Group 5, 75 per cent. in Group 7 and 100 per cent. in Group 8 obtained poor results.

21. Fifty per cent. of the patients without metastasis operated on in Group 1, and 65.38 per cent. of those in Group 2 obtained good results; while 50 per cent. in Group 1, 30.76 per cent. in Group 2, 100 per cent. in Group 3, 100 per cent. in Group 4 and 100 per cent. in Group 7 obtained poor results. In Group 2, 3.84 per cent. obtained fair results.

22. Of the patients operated on without removal of the regional lymph nodes and salivary glands, 33.33 per cent. in Group 1, 18.75 per cent. in Group 2, 50 per cent. in Group 4, 54.54 per cent. in Group 5 and 25 per cent. in Group 7 obtained good results; while 66.66 per cent. in Group 1, 81.25 per cent. in Group 2, 100 per cent. in Group 3, 50 per cent. in Group 4, 45.45 per cent. in Group 5, 75 per cent. in Group 7 and 100 per cent. in Group 8 obtained poor results.

23. In all the groups in which metastasis was demonstrated, good results were obtained by 5.71 per cent. of the patients, and poor results by 94.28 per cent. The average duration of the lesions was 0.966 years, and the average size of the lesion, 3.695 cm. The average duration of life since the last or only operation on patients who are living with a good result is 6.57 years. The one patient who obtained a good result, but died later from some cause other than epithelioma, lived 6.16 years, and those in whom the result was poor died after an average of 0.74 years.

24. In all the groups in which metastasis was not demonstrated, good results were obtained by 53.33 per cent. of the patients, fair results by 2.22 per cent. and poor results by 44.44 per cent. The average duration of the lesion was 1.4 years, and the average size of the lesion, 3.39 cm. The average duration of life since the last or only operation of the patients who are living with good results is ten years, and the one patient in whom the result was fair is living 10.63 years after the last operation. The patients who obtained good results, but subsequently died from some cause other than epithelioma lived 5.71 years, and the patients in whom the result was poor lived 1.8 years.

25. In all the groups in which the regional lymph nodes and salivary glands were not removed, good results were obtained by 27.41 per cent. of the patients, and poor results by 72.58 per cent. The average duration of the lesion was 1.05 years and the average size 3.75 cm. The average duration of life since the last or only operation in patients still

living with a good result is 8.69 years; in those who died with a poor result, 1.23 years.

26. By comparing Conclusions 23, 24, and 25, it will be seen that the patients in whom metastasis was demonstrated had lesions that had existed on an average of 0.43 of a year less than those in whom metastasis was not demonstrated, and that the lesion was 0.3 cm. larger. Moreover, only one-ninth as many good results were obtained, and more than twice as many poor results. Also the patients with poor results lived on an average of 1.06 years less after the last or only operation than those with poor results, but without evidence of metastasis. The patients in whom no regional lymph nodes or salivary glands were removed took a middle position on each of the points mentioned, except the size of the lesion.

27. Of the patients in Group 1, 15.90 per cent. are alive with good results, and have been free from the disease for an average of 8.59 years.

28. Of the patients in Group 1, 4.54 per cent. obtained good results, and had been free from the disease an average of 7.07 years at the time of death.

29. In Group 1, 20.44 per cent., or about one in five of the patients obtained good results.

30. In Group 1, 79.54 per cent. of the patients obtained poor results, and lived an average of 0.917 year.

31. In Group 2, 25.28 per cent. of the patients are alive with good results. They have been free from the disease for an average of 9.66 years.

32. In Group 2, 3.44 per cent. of the patients obtained good results, and had been free from the disease an average of 4.8 years at the time of death.

33. In Group 2, 28.73 per cent. of the patients obtained good results.

34. In Group 2, 1.14 per cent. of the patients are alive with fair results.

35. In Group 2, 70.11 per cent. of the patients obtained poor results. They lived for an average of 1.06 years.

36. One hundred per cent. of the patients in Group 3 obtained poor results, and lived an average of 1.48 years.

37. In Group 4, 16.66 per cent. of the patients are alive, with good results, and have been free from the disease for 11.15 years.

38. In Group 4, 16.66 per cent. of the patients obtained good results.

39. In Group 4, 83.33 per cent. of the patients obtained poor results. They lived for an average of 1.83 years.

40. In Group 5, 46.66 per cent. of the patients are alive with good results and have been free from the disease for an average of 8.24 years.

41. In Group 5, 46.66 per cent. of the patients obtained good results.

42. In Group 5, 53.33 per cent. of the patients obtained poor results, and lived for an average of 0.635 year.

43. In Group 7, 14.28 per cent. of the patients are alive with good results, and have been free from the disease for an average of 7.98 years.

44. In Group 7, 7.14 per cent. of the patients obtained good results, and had been free from the disease for 6.16 years at the time of death.

45. In Group 7, 21.42 per cent. of the patients obtained good results.

46. In Group 7, 78.57 per cent. of the patients obtained poor results. They lived an average of 0.98 of a year.

47. One hundred per cent. of the patients in Group 8 obtained poor results. They lived an average of 0.358 of a year.

48. In a consideration of all the groups from the standpoint of grade of malignancy relative to mortality, and exclusive of deaths from unknown causes and postoperative deaths, epithelioma was the cause of death in 75 per cent. of patients with Grade 1 malignancy, in 93.22 per cent. with Grade 2, in 98.3 per cent. with Grade 3, and in 100 per cent. with Grade 4.

49. The total good results for all groups were: 72.72 per cent. in cases of Grade 1 malignancy; 34.88 per cent. in cases of Grade 2 malignancy; 9.37 per cent. in cases of Grade 3 malignancy, and 6.25 per cent. in cases of Grade 4 malignancy.

50. The total fair result was 1.16 per cent. for Grade 2 malignancy.

51. The total poor results for all groups were 27.27 per cent. for Grade 1 malignancy, 63.95 per cent. for Grade 2, 90.62 per cent. for Grade 3 and 93.75 per cent. for Grade 4.

52. Of the patients with metastasis, 38.09 per cent. had Grade 2 malignancy; 52.38 per cent., Grade 3, and 9.52 per cent., Grade 4.

53. Of the patients without metastasis, 9.09 per cent. had Grade 1 malignancy; 60.6 per cent., Grade 2; 24.24 per cent., Grade 3, and 6.06 per cent., Grade 4.

54. Of the patients in whom the regional lymph nodes and salivary glands were not removed, 11.62 per cent. had Grade 1 malignancy; 50 per cent., Grade 2; 27.9 per cent, Grade 3, and 10.46 per cent., Grade 4.

55. Of all the patients, 22.03 per cent. are alive, with good results. They have been free from the disease for an average of 9.16 years; 3.38 per cent. of the patients obtained good results and had been free from the disease for an average of 5.78 years at the time of death; 25.42 per cent. obtained good results; 0.56 per cent. obtained fair results, and 74.01 per cent. obtained poor results and lived for an average of 1.078 years.

THE RELATIONSHIP BETWEEN THE PATHOLOGIC AND CLINICAL ASPECTS OF THE DISEASES OF THE THYROID GLAND*

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Any attempt to correlate the clinical and pathologic aspects of the thyroid gland encounters many difficulties. At present it is almost impossible to visualize just what may be considered the normal thyroid at various ages and under various conditions of environment, because the gland is quickly and markedly affected by external stimuli. McCarrison [1] has shown that certain variations in food, especially if the food supply is improper or defective, cause a marked change in the histology of the gland. It has also been shown that the structure of the gland varies during different physiologic states, such as puberty, menstruation and pregnancy. Isenschmid [2] and Damberg [3] have shown that the histologic appearance of the thyroid varies according to the geographical habitat of the individual. A gland that would be considered normal in a native of the mountainous regions of Bern would not be regarded as normal if found in a resident of Kiel (sea-level), although in both cases the glands were removed from normal persons whose deaths were caused by an extrathyroid condition.

The etiology of the various histologic pictures found in the thyroid, whether attended by symptoms or not, is still unknown. The question as to whether these changes are due to a primary condition in the gland or whether the thyroid is simply a secondary factor in some systemic condition, is still unsettled. Wilson,[4] in a recent article, sums up the matter, particularly with regard to exophthalmic goiter, as follows:

> The changes in the cervical sympathetic ganglia, in the cortical brain cells, in the heart muscle and in a number of the skeletal muscles are uniformly present in persons who have died from exophthalmic goiter. . . . Further-

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* Read before the surgical section of the Academy of Medicine, May, 1924.

1. McCarrison: The Thyroid Gland in Health and Disease, William Wood & Co., 1917.

2. Isenschmid, R.: Zur Kenntnis der Menschlichen Schild-drüse in Kindes alter, Frankfurt. Ztschr. f. Path. **5**:205, 1910.

3. Damberg, E. S.: Die Schilddrüsen vom 15-25 Lebensjahr aus der Nordeutschen Ebene und Kustengegend so wie aus Bern, Frankfurt. Ztschr. f. Path. **6**:312, 1910-1911.

4. Wilson, L. B.: Collected Papers of the Mayo Clinic **14**:448, 1922.

more, in the present state of our knowledge we are not warranted in assuming that all changes, particularly those of the cervical sympathetic ganglia, are necessarily secondary to changes in the thyroid itself.

A purely pathologic classification of the affections involving the thyroid is almost impossible. Again, if one attempts a clinical classification of the various symptom complexes associated with disease of the thyroid, one finds a large number of cases which, although symptomatically resembling one another, have a totally different pathologic basis and require a correspondingly different treatment. For practical purposes, therefore, I grouped the affections of the thyroid gland from the therapeutic standpoint, recognizing that, at best, this is only of temporary application, since the treatment may change at any time.

1. Cases that are purely medical.
   a. Cretinism.
   b. Myxedema.
   c. Adolescent goiter.
2. Cases requiring both medical and surgical treatment.
   a. Exophthalmic goiter.
   b. Colloid goiter with or without toxic symptoms.
   c. Cretins with goiter.
   d. Congenital goiter.
   e. Acute thyroiditis.
   f. Acute strumitis.
3. Cases that are purely surgical.
   a. Adenomas—toxic and nontoxic.
   b. Thyroid enlargements causing mechanical obstruction.
   c. Malignant growth.

This study is based upon the examination of 185 thyroids. Any enlargement of the thyroid gland is regarded as "goiter."

Congenital goiter	4
Cretin thyroid	3
Adolescent goiter	4
Colloid goiter	36
Adenoma:	
Colloid 4 / Fetal 80	84
Exophthalmic goiter	51
Malignancy of the thyroid	3

CRETINS

Cretins without goiter usually have no recognizable thyroid or only a remnant of the gland. In the three cretin thyroids examined, 34, 38, and 39 years of age respectively, the gland consisted of a piece of tissue about 4 by 1 cm., very hard, and of a grayish appearance. Microscopic examination showed a very dense stroma with a marked increase in the

amount of connective tissue. The gland was divided into lobules by connective tissue bands. From these trabeculae many fine strands were given off, which seemed to invest each vesicle with a layer of connective tissue. If the section is stained by the Van Gieson method, these fine connective tissue strands can be demonstrated (Figs. 1, 2, 3, 4 and 5).

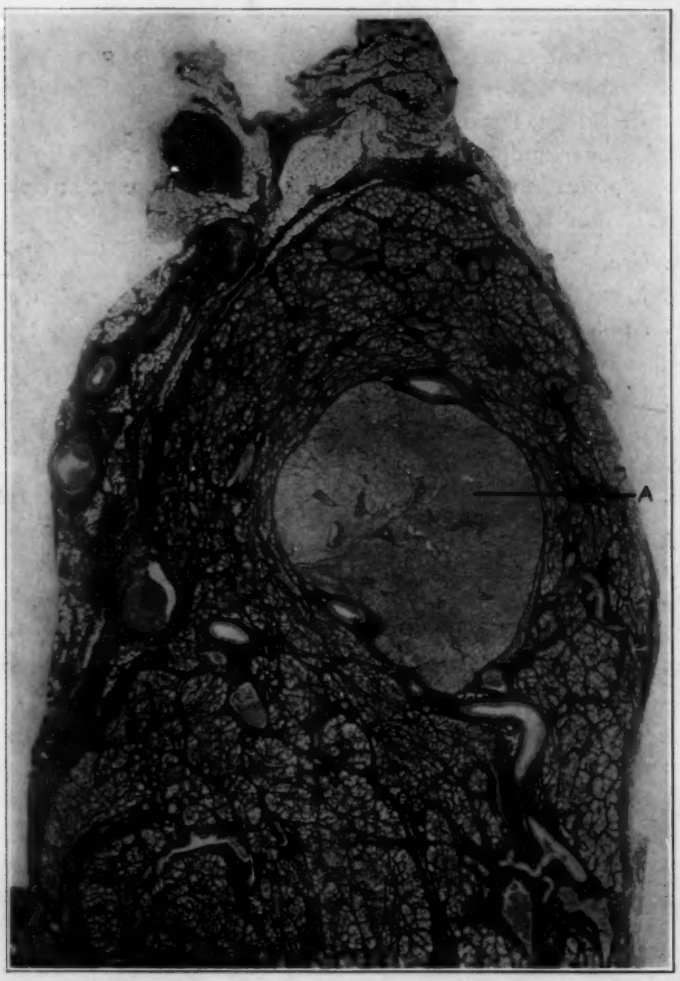

Fig. 1.—Cretin thyroid A, showing marked increase in the connective tissue; *A*, parathyroid buried in the substance of the thyroid.

Occasionally one sees in the stroma some parenchyma cells (interstitial cells).[5]

5. The term "interstitial cells" is applied to certain cells found in the stroma, the exact nature and function of which are not known. These cells closely resemble the fully differentiated cells lining the acinus.

The acini are small; in some sections, they are normal in number (cretin A); in others, they are few (cretin B). In some glands, the acini are filled with colloid; in others, it is absent. The cells lining the colloid containing acini are low, cuboidal, or flat. In the acini that contain no colloid, there is no regularity in the arrangement of the epithelial cells. The cells appear to be desquamating into the lumen of

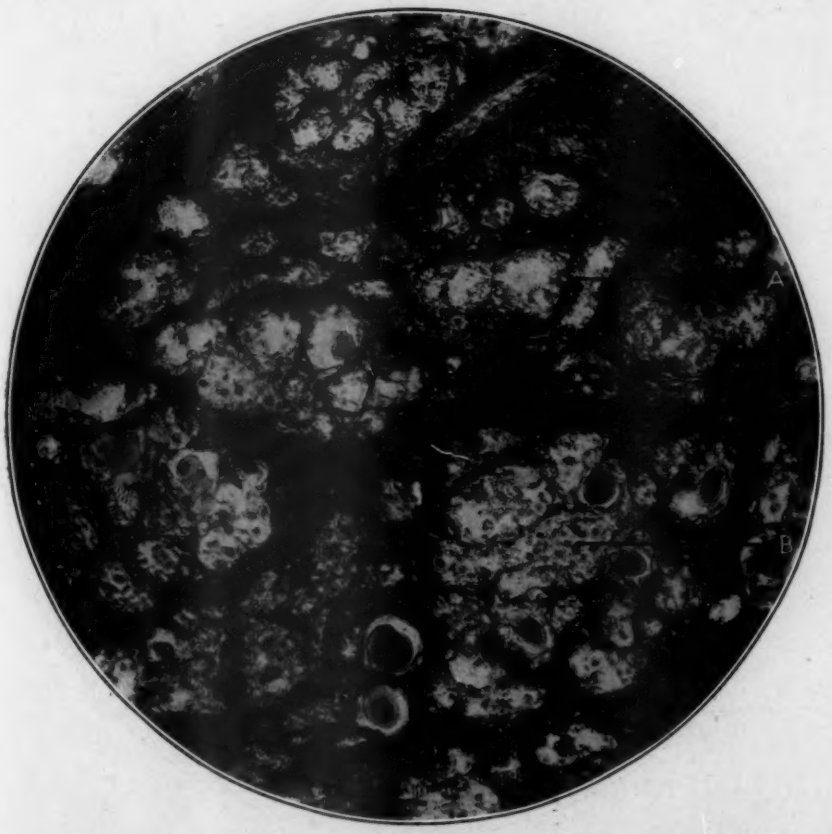

Fig. 2.—Cretin thyroid A (high power). The increase in connective tissue is clearly seen. *A*, connective tissue strands investing each vesicle; *B*, cells appear to have desquamated into the lumen of the acini.

the acini. The cytoplasm of the epithelium is granular, and the cell outlines are not clear; they are neither sharply demarcated from the lumen nor from each other. The nuclei appear swollen and seem to be degenerating; the colloid, when present, stains very deeply. In several areas, colloid seems to be lying free in the connective tissue spaces. These are probably acini from which the epithelium has disappeared. From the clinical and pathologic examination of these cases, one is led

to the conclusion that these glands either do not function normally or do not function at all.

CONGENITAL GOITER

There were four cases of congenital goiter in this series; all these patients died during or shortly after birth. In two of our cases, we were able to obtain the whole gland. Grossly, the glands were sym-

Fig. 4.—Cretin thyroid B, showing marked increase in connective tissue; *A*, cells lining acini distinctly flattened. Acini seem to be fewer than in cretin gland A. Colloid stains very deeply.

metrically enlarged, each lobe measuring 4 by 5 by 3 cm. The surface was lobulated. On section, the gland presented a solid mass of tissue with only an occasional area of colloid.

Microscopic section shows an increase in the connective tissue stroma that divides the gland into lobules, and from these bands fine strands enter directly into the lobule. The acini may be well formed; the arrangement may be fairly normal. The epithelium lining the acini

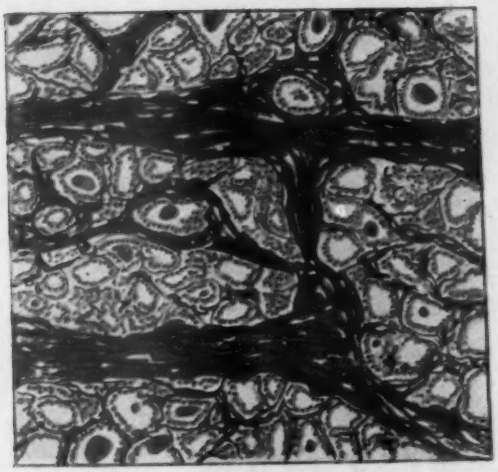

Fig. 3.—Cretin thyroid A (Van Gieson), low power, showing connective tissue dividing gland into lobules and strands of connective tissue investing the individual acinus.

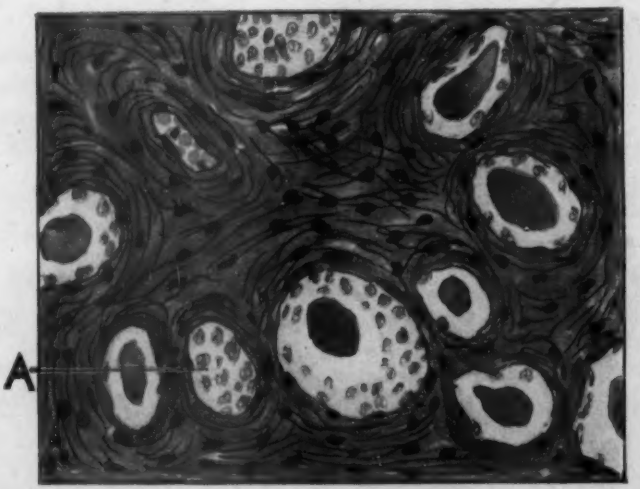

Fig. 5.—Cretin thyroid B (Van Gieson), high power, showing thyroid containing large amount of connective tissue; *A*, desquamated cells in the lumen of the acinus.

may be columnar and occur in a single layer; the cells may be sharply demarcated from the lumen and from each other (Fig. 6) or they may be in many layers almost filling the entire cavity of the acinus, giving the impression that the entire lobule is solid (Fig. 7). In the former type, there seems to be a marked proliferation of the epithelial cells in the stroma (interstitial cells). In the latter, no interstitial cells are seen. In most of the sections, the acini contain little or no colloid. Histologically, these glands convey the impression of a functioning organ.

MYXEDEMA

Myxedema may be the result of too much surgery upon a goitrous gland, or it may be found in a patient whose thyroid has undergone degeneration to such an extent that sufficient functioning thyroid is not present to supply physiologic needs. I have no section of such a gland.

ADOLESCENT GOITER

The slight or moderate thyroid enlargements which are seen in young women between the ages of about fourteen and twenty-three, and which frequently disappear with small doses of iodid or without any treatment, are called adolescent goiters. These cases rarely come to operation, and it is through the kindness of Dr. Goetsch and Dr. Heyd that we are able to describe the histopathology of such glands. In our limited experience, three types were found: first, the simple colloid adolescent goiter; second, the hyperplastic adolescent goiter; and third, the colloid adolescent goiter with small adenomas.

The colloid type presents clinically, a symmetrical, smooth enlargement of the thyroid. Generally, this is not great, yet the patients usually seek advice on account of the fulness in the neck. As a rule, they present no other symptoms. Histologically, an arrangement very similar to that seen in simple diffuse colloid goiter is found. The acini are of varying sizes and are filled with colloid; the epithelium is flattened, and the stroma seems to be diminished. Rupture of the wall of the acinus with the formation of microcysts may occur. The gland appears to be in a state of low activity (Fig. 8).

In the hyperplastic type, the patients present clinical disturbances in addition to the local deformity, which distinguishes them from the colloid type. They complain especially of varying degrees of nervousness. There is usually little, if any, rise in the basal metabolic rate, while the Goetsch test may be mildly positive or negative. Histologically, the acini are found to be filled with colloid, but the epithelial cells, instead of being flat, as in the colloid type, range from cuboidal to columnar. These cells seem to be increased in number as well as in size, and in some areas the epithelium appears to be plicated. Many

areas containing apparently new-forming acini are seen. These acini are small, filled with colloid, and lined by cuboidal epithelium. There is also an apparent proliferation of epithelial cells (interstitial cells) in the stroma (Fig. 9). From a study of the histologic and clinical picture in these cases, there is some question as to whether we are not in some instances dealing with an early exophthalmic goiter, varying from true exophthalmic goiter only in degree.

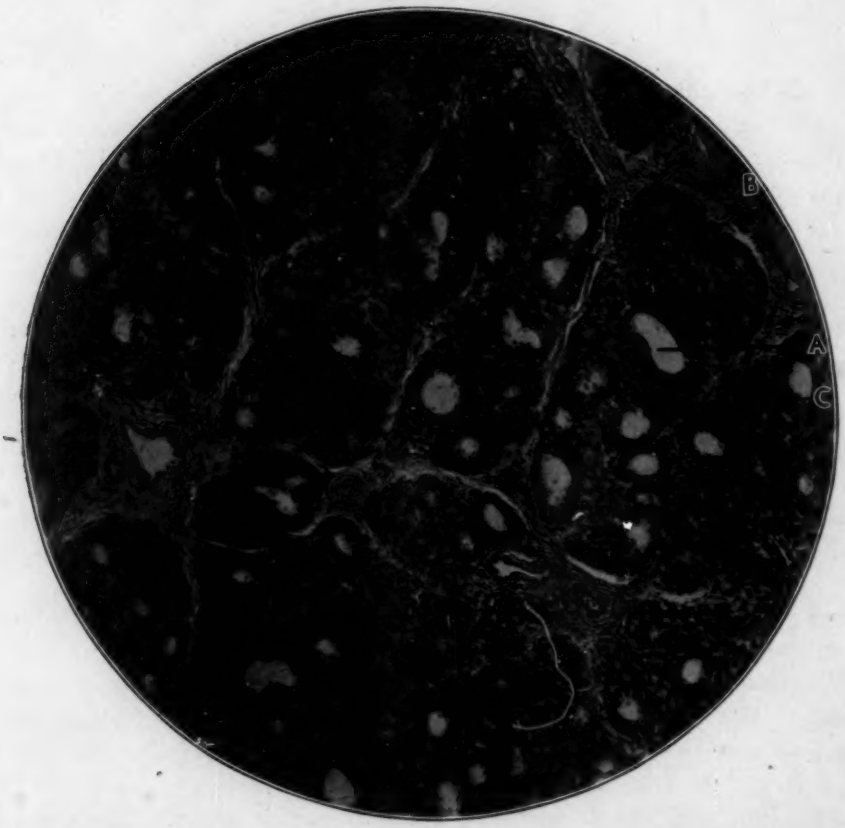

Fig. 6.—Congenital goiter; *A*, well formed acini; *B*, increase of connective tissue; *C*, proliferation of epithelial cells in stroma (interstitial cells).

The third type, the adolescent goiter with small adenomas, presents the same clinical picture as the adolescent colloid goiter. Under treatment there is a general reduction in the goiter, and one or more small adenomas which previously were not felt become prominent. Histologically, the thyroid presents the same appearance as the adolescent colloid goiter, except that several small encapsulated adenomas are found in the gland.

There is some question as to whether the enlargements of the thyroid seen at puberty in the vicinity of New York are the same as those seen in the Great Lakes region in the United States, and in the goitrous belts of Switzerland. Comparing the clinical course of the local cases with those occurring elsewhere, one is led to believe that the adolescent goiters of the Great Lakes and Switzerland are pathologic enlargements

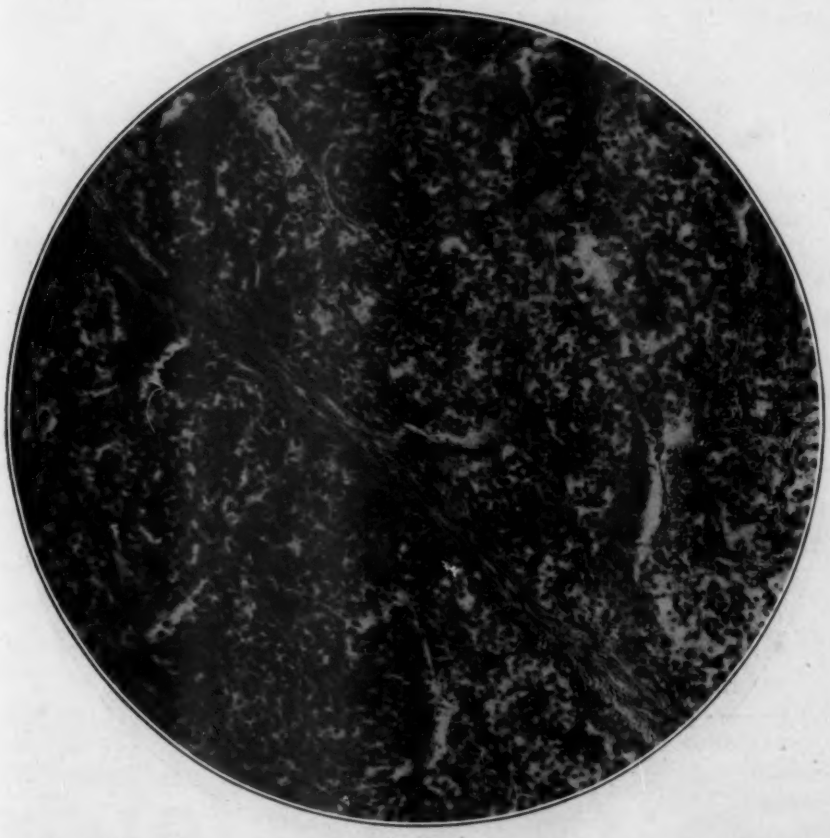

Fig. 7.—Congenital goiter (second type). Cells lining the acinus found in many layers almost filling the entire cavity.

due to a definite etiologic factor, while the enlargements seen in New York are physiologic enlargements due to an increased demand by the general system upon the thyroid. This, I believe, is borne out by the fact that the administration of small doses of iodid to the patients in the Great Lakes region and in Switzerland gives such excellent results, while in New York we are under the impression from a study of a limited number of cases that the results have not been so uniformly successful.

EXOPHTHALMIC GOITER

No type of goiter has caused as much discussion as exophthalmic goiter. This disease has been classified as one which requires both medical and surgical treatment. In the condition regarded as exophthalmic goiter, a definite pathology is usually found which varies but little.

Grossly, the gland is symmetrically enlarged, somewhat lobular in appearance, with large blood vessels coursing over its surface. On

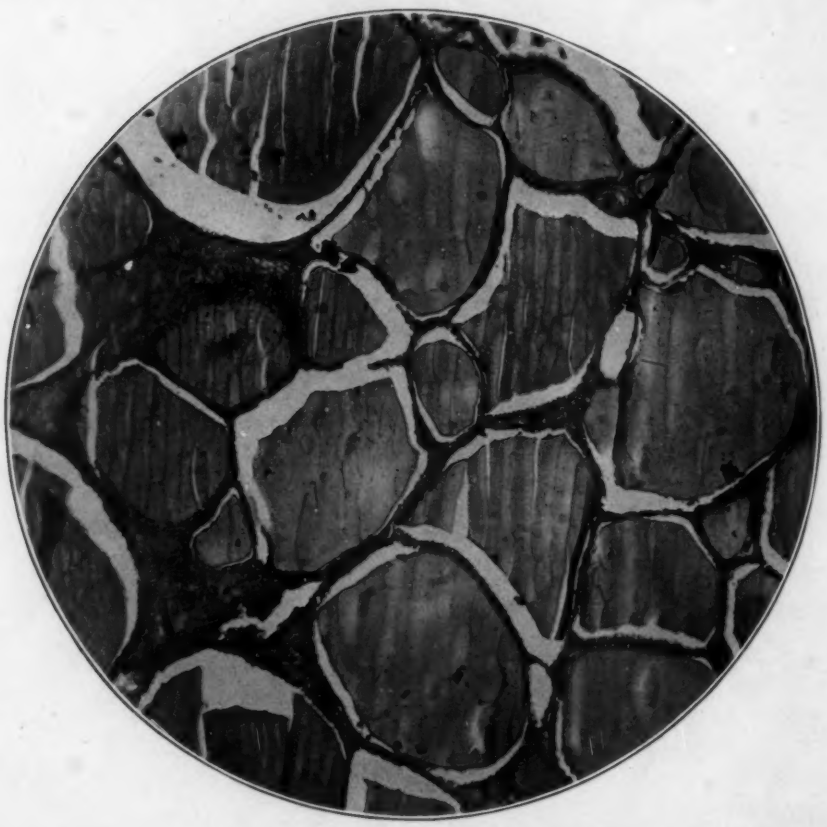

Fig. 8.—Adolescent colloid goiter.

section, it presents a solid mass of tissue, grayish pink in color; there is usually no glistening colloid present, and the surface is opaque. Microscopically, the blood vessels are markedly dilated; the acini are very irregular in shape, with a moderate amount of stroma between them. In the stroma, there are many cells resembling parenchyma cells of the acini. These are sometimes called interstitial cells. Areas of round-celled infiltration are also seen in the stroma (Fig. 10). In some places, these areas are small; in others, the formation of apparent germinal

centers is present. The parenchyma cells lining the acini are increased in size and numbers; they are high columnar, instead of flattened or cuboidal. The epithelium appears to be thrown into folds forming irregular, papillary-like ingrowths into the cavity of the acini. These papillary-like ingrowths may almost fill the acinus cavity. The cytoplasm of the parenchyma cells is quite granular, and the nuclei are usually swollen and take a very deep stain. If treated with a special stain, the mitochondria content of these cells seems noticeably increased. The colloid in the acini is scant and thin or entirely absent. This microscopic picture, particularly hypertrophy and hyperplasia of the epithelium, papillary-like ingrowths, increased vascularity, scant and thin colloid, is the one which we have observed in practically every case clinically diagnosed as exophthalmic goiter (Fig. 11).

Wilson [6] goes even a step further and says that not only has exophthalmic goiter a definite pathology, but that in 80 per cent. of the cases he can estimate the stage to which the exophthalmic goiter has advanced from the gross and microscopic appearance of the removed tissue.

I have not as yet been able to reach this conclusion; I have, however, observed in several cases of exophthalmic goiter that have lasted for eighteen months or more, an increase in the amount and the density of the colloid in the acini. This increase is marked and definite, even though the papillary-like projections remain. This same change has also been observed in two patients with exophthalmic goiter on whom a hemithyroidectomy had been performed and who were again operated on for a recurrence of symptoms. Since there has not been a sufficient number of these cases, it is not possible to judge what inference should be drawn from these observations.

Clinically, which cases should be diagnosed as exophthalmic goiter? This syndrome is characterized by a variable group of symptoms, the chief of which are enlargement of the thyroid, exophthalmos, tachycardia, and tremor. The grouping and development of these symptoms is very variable; the onset is relatively acute; the course is chronic and is characterized by remissions and exacerbations.

Plummer [7] states that "if the average course of the disease be presented by a curve, the greatest height of the intoxication is found to be reached during the latter half of the first year and then rapidly drops to the twelfth month. Secondary symptoms and exophthalmos may remain, but the active course rarely continues over four years without distinct intermissions."

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6. Wilson, L. B.: The Pathology of the Thyroid Gland in Exophthalmic Goiter, Am. J. M. Sc. **146**:781, 1913.

7. Plummer, quoted by Mayo: Collected Papers of the Mayo Clinic **4**:509, 1912.

The various forms of goiter that have existed for from eight to sixteen years before they have produced marked toxic symptoms are not classified as exophthalmic goiter, even though the clinical syndrome be practically the same. It is at this particular point that the clinician and the pathologist differ most. The clinician frequently designates as exophthalmic goiter an adenoma, which has begun to cause toxic symptoms such as nervousness, tremor and tachycardia. This condition is

Fig. 9.—Adolescent goiter, hyperplastic type; *A*, cuboidal epithelium lining acini, *B*, interstitial cells.

not exophthalmic goiter; it is a toxic adenoma. These two syndromes must be clearly differentiated from one another because their pathology and treatment are dissimilar.

COLLOID GOITER

Colloid goiter is met with frequently. It is the usual form of endemic goiter and is the type that gives the largest goiters with the fewest toxic symptoms. Grossly, there are two forms; first, the diffuse

colloid goiter, seen particularly as one type of adolescent goiter in which the gland is diffusely and symmetrically enlarged; second, the large, irregular nodular type found in women who have had a goiter for many years.

Gross examination of the goiter reveals a peculiar, glistening, honeycombed structure. This appearance is caused by the presence of colloid in various quantities in the acini. The acini are of various sizes and

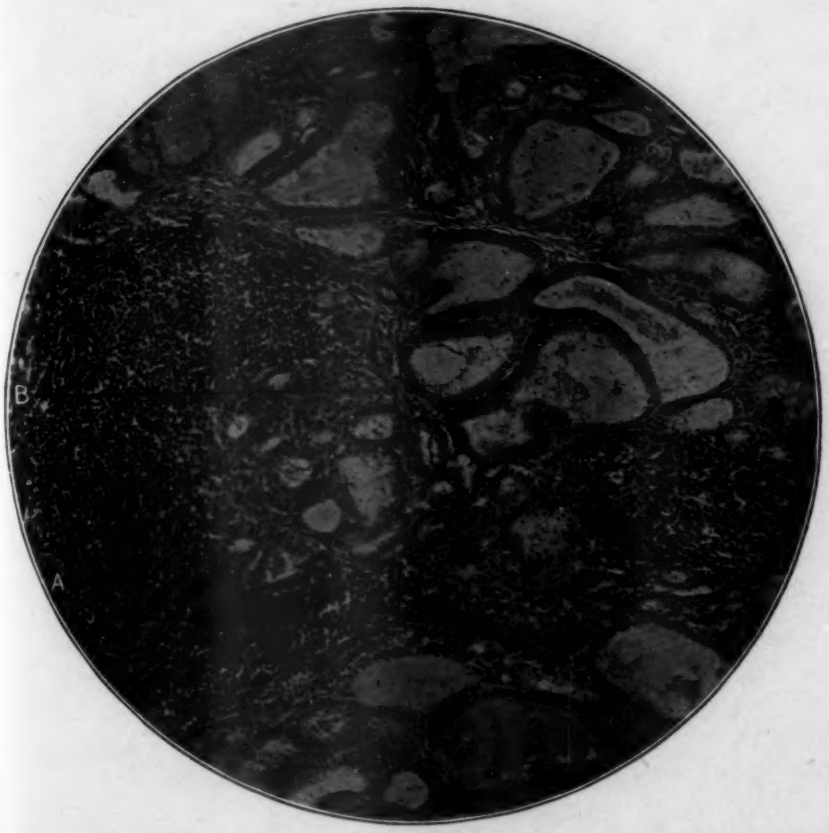

Fig. 10.—Exophthalmic goiter. *A*, round cell infiltration; *B*, hyperplasia of parenchyma cells in the stroma (interstitial cells).

shapes. Cysts may be found filled with colloid. Microscopically, one sees alveoli distended with colloid. The parenchyma cells are distinctly flattened; the walls of the acini frequently break down, allowing two or more to coalesce, forming microcysts. The stroma is very scant (Fig. 12). In some areas, it seems to have undergone hyaline degeneration. One finds connective tissue bands running through the section. Occasionally, close to these connective tissue bands or to the capsule, some

apparently new-forming acini are seen. These present themselves as an accumulation or piling up of embryonal or cuboidal parenchyma cells and a formation of small acini lined by cuboidal epithelium, sometimes filled with colloid. L. B. Wilson regards this regeneration as characteristic of clinical cases that present a history of long standing enlargement of the thyroid, with subsequent slow development of toxic symptoms. In four of the colloid goiter cases presenting toxic symptoms, desig-

Fig. 11.—Exophthalmic goiter. Irregular size and shape of acini, *A*; papillary-like ingrowths, *B*; colloid scant.

nated "quite nervous," "irregular heart," "irritable," "nervous," several areas of these apparently new-forming alveoli (Fig. 13) were found.

ADENOMA

Adenomas of the thyroid are frequent; in a series of sixty-five cases from one clinic, thirty-six presented adenomas. They are usually classified, histologically, as fetal or adult adenomas. From the clinical standpoint, this is unnecessary because there is no difference in their

symptomatology. Crile classifies all adenomas as fetal, following Wölfler, who believes that they arise from fetal rests. Crotti [8] also regards them as being congenital in origin. He does not believe that the normal parenchyma of the gland takes any part in their formation. Adenomas are often multiple, occurring throughout both thyroid lobes. Forty-five per cent. of the cases at the Mayo Clinic were multiple

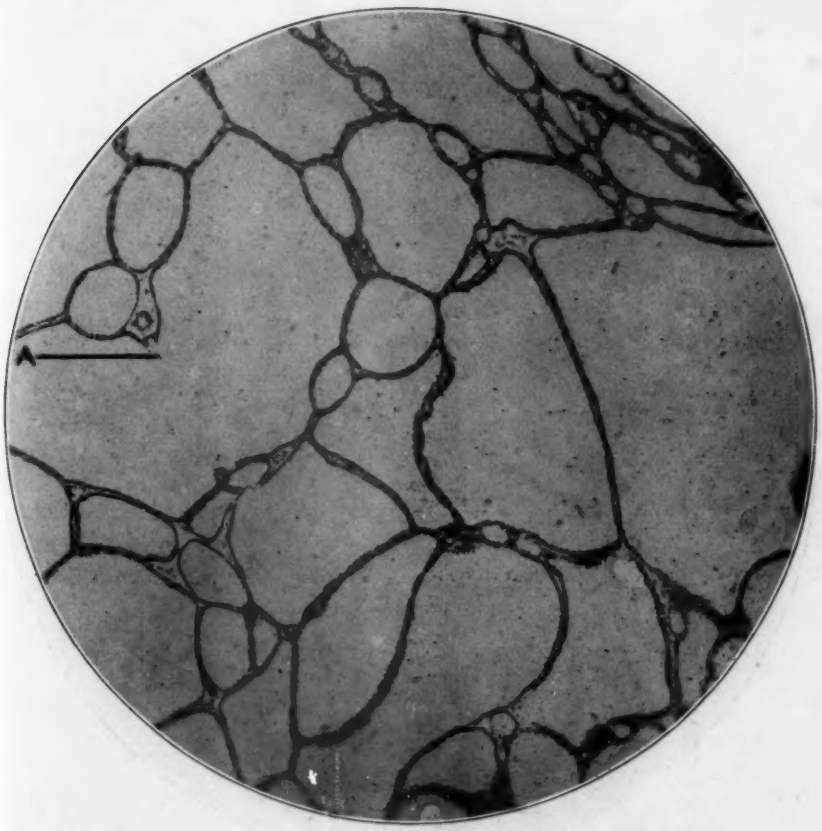

Fig. 12.—Colloid goiter. The acini are distended with colloid, the epithelium flattened, and there is scant interacinal stroma. *A*, coalescence of two acini to form microcyst.

(Balfour [9]). Adenomas are single or multiple, small, round, sharply demarcated, freely movable, painless bodies of firm consistency. They vary in size from several millimeters to 5 and 10 cm. in diameter.

Clinically, most writers state that the adenomas give no toxic symptoms until they have existed for many years (from eight to sixteen

8. Crotti, A.: Thyroid and Thymus, Philadelphia, Lea & Febiger, 1918.
9. Balfour, D. C.: Collected Papers of the Mayo Clinic **6**:363, 1914.

years). I do not agree with this. I believe, from a study of the cases presented, that if the history of these patients were carefully analyzed one would often find nervousness, irritability, tachycardia, palpitation, a lowered nervous threshold, etc., quite frequently short of eight years of onset. In seventeen out of sixty-five cases of adenoma clinically diagnosed "adenomatous goiter," or "obstructive goiter," nontoxic, among the symptoms noted were tremor, ranging from slight to extreme,

Fig. 13.—Colloid goiter, showing *A*, small, probably new forming acini, and *B*, hyaline degeneration of the stroma.

rapid pulse and eye signs. I believe these symptoms are due to a mild toxic condition. This toxemia may be so mild that it causes no rise in the metabolic rate. Whether the toxic substances giving rise to these symptoms come from the adenomas or are caused by a change in the secretion of the thyroid, due to the presence of the adenoma, we are not prepared to say, but these symptoms usually disappear shortly after the tumors are removed.

All adenomas are circumscribed, and present a rather dense connective tissue capsule. This capsule may or may not have undergone some of the various types of degeneration (hyaline, calcareous). The adenomas as a rule shell out very readily.

Histologically, one may find within adenomas practically any pathologic picture that occurs in the thyroid gland, depending on the cell proliferation and the type of degeneration which the adenoma has

Fig. 14.—Adenoma (fetal type), showing *A*, thick connective tissue capsule; *B*, solid alveoli.

undergone. The usual type is the fetal or adult adenoma, according to its histologic appearance. A very small percentage of adenomas are pure colloid (2 per cent., according to a personal communication from Goetsch). Solid tumors have also been observed in our series.

In the fetal adenomas one sees numerous small alveoli lined by cuboidal epithelium with or without colloid and some solid cords of apparently new-forming acini (Fig. 14). The stroma in these cases frequently shows marked hyaline degeneration. In the adult type

the gland closely resembles the normal adult thyroid with its moderately large acini filled with colloid and lined by cuboidal epithelium. These adenomas may undergo hyaline, myxomatous, and calcareous degeneration.

The colloid adenomas have the typical appearance of colloid goiter, showing large acini filled with colloid, a distinctly flattened epithelium, and a very scant stroma. Along the edges of the capsule in long stand-

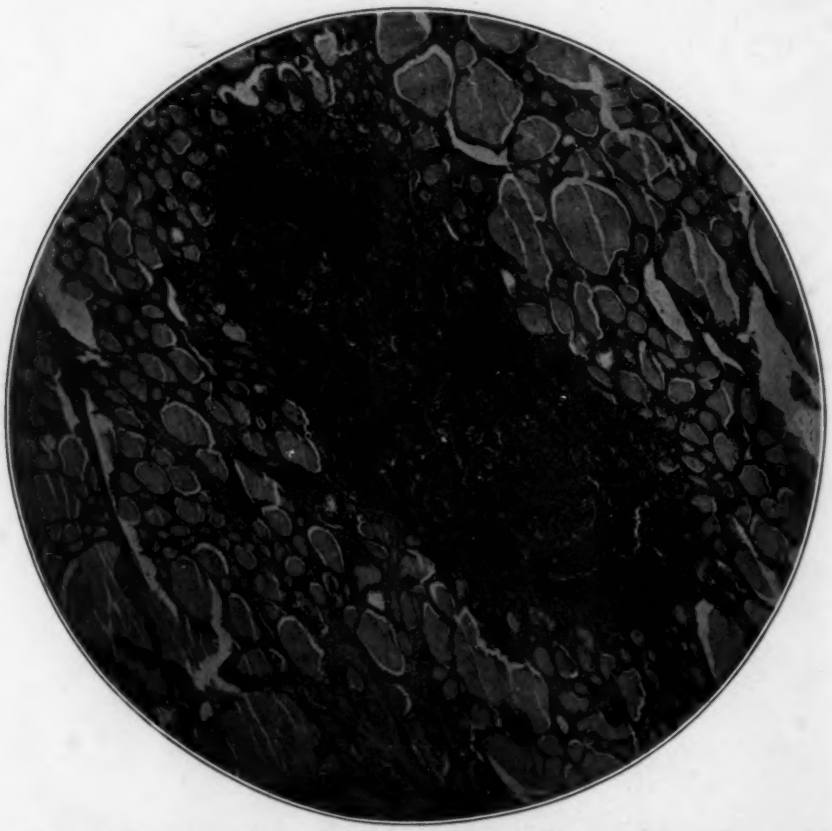

Fig. 15.—Round celled infiltration in an adult adenoma of the thyroid, showing the formation of an apparent germinal center. Clinically, this patient presented toxic symptoms.

ing cases one may find apparently regenerating acini. In adenomas this is also interpreted as a sign of slowly developing toxicity.

Whether or not one can differentiate, histologically, toxic from nontoxic adenomas is doubtful; one cannot weigh the reactivity or the compensatory power of an individual from a histologic picture alone. The lesion in the gland may be very slight, but owing to a lowered compensatory power on the part of the individual the symptoms may

be very marked. I believe that from the amount of round-celled infiltration found in the adenoma and in the remaining apparently normal thyroid tissue, one may at times be able to differentiate toxic from nontoxic adenomas. This is not absolute but has proved positive in a large percentage of our cases. The degree of toxicity, however, cannot be estimated. This lymphocytic infiltration occasionally appears to form actual germinal centers (Fig. 15).

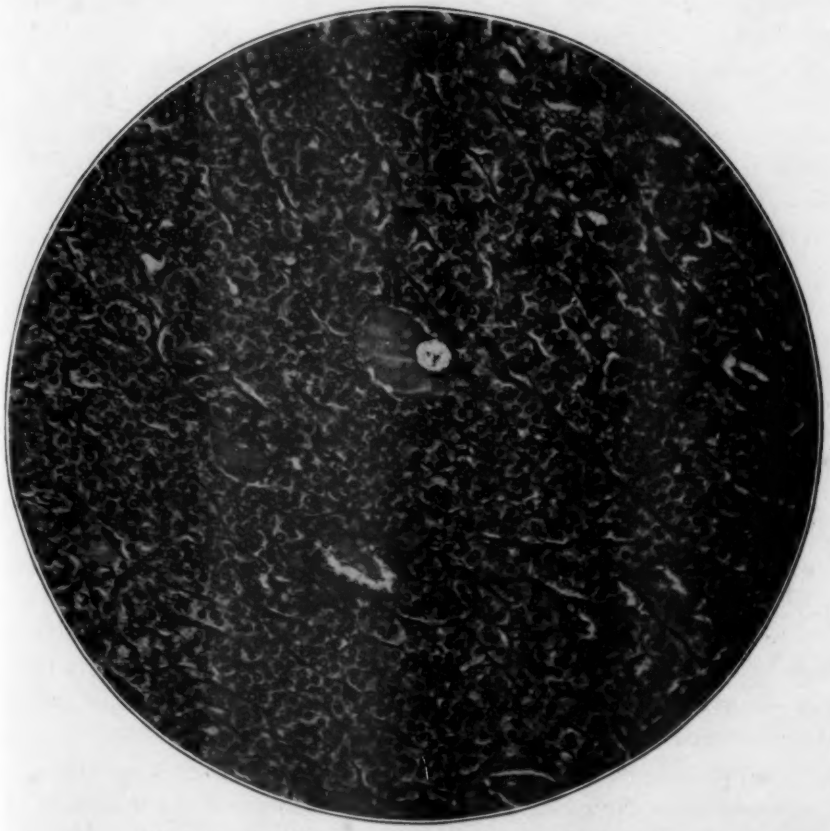

Fig. 16.—Solid adenoma of thyroid, nonmalignant.

The solid adenomas, histologically, may closely resemble malignant tumors (Fig. 16). One should not designate these solid adenomas as malignant unless, first, some evidence of infiltration of the capsule is seen; second, metastases have developed, and third, the tumor has recurred after removal.

MALIGNANT TUMORS OF THE THYROID

Histologically, the diagnosis of malignant tumors of the thyroid is difficult on account of the marked metaplasia the cells of the thyroid

may undergo. Areas of thyroid tissue may be found in some cases of exophthalmic goiter (two in our series) in which the papillary-like ingrowths so completely fill the acini as to give the appearance of a malignant tumor. In the solid nonmalignant adenomas of the thyroid there may be an encapsulated tumor with a growth of epithelial cells, without any apparent acini formation, and which gives neither metastases nor recurrence after removal. Yet on microscopic appearance, one receives the impression of a malignant tumor. One such case occurred in the series discussed here.

Clinically, malignant tumors of the thyroid are diagnosed by the appearance of a hard tumor in a previously normal thyroid or a sudden increase in size of a goiter which had remained constant for many years, by the onset of symptoms showing the involvement of the surrounding structures by an infiltrating mass, or by the appearance of distant or local metastases.

Jaeger,[10] in comparing the histologic variation between the primary and the secondary tumors, found that: (*a*) both primary and secondary tumors may appear benign; (*b*) the primary tumor may show a malignant change and the metastases appear benign; (*c*) the primary tumor may appear benign, and the secondary tumor show distinct signs of malignancy; (*d*) both the primary and secondary tumors may appear malignant.

In this series there were only three definitely malignant tumors, one sarcoma, and two carcinomas.

CONCLUSIONS

1. For therapeutic purposes the diseases of the thyroid gland may be divided into three groups: (1) The purely medical cases; (2) the cases requiring both medical and surgical treatment, and (3) the purely surgical cases.

2. A definite pathologic picture was observed in every case clinically diagnosed as exophthalmic goiter; i. e., hypertrophy and hyperplasia of the epithelium, papillary-like ingrowths, increase in size and number of blood vessels, scant and thin colloid.

3. The various forms of goiter that have existed for from eight to sixteen years before they have produced marked toxic symptoms are not classified as exophthalmic goiter, even though the clinical syndrome be practically the same as that seen in exophthalmic goiter. These two syndromes must be clearly differentiated from each other because their pathology and treatment are so dissimilar.

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10. Jaeger, quoted by Ewing: Neoplastic Diseases, W. B. Saunders Company, 1919.

ENCHONDROMA OF THE FEMUR WITH REPEATED RECURRENCES AND ULTIMATE DEATH

REPORT OF CASE

ROBERT G. LeCONTE, M.D.; WALTER ESTELL LEE, M.D.,
AND
WILLIAM P. BELK, M.D.
PHILADELPHIA

In view of the great interest that is being taken at the present time in the study and classification of bone tumors, it seems justifiable to place this case on record. The patient first came under observation in 1909, and death occurred three years later, in 1912. At that time, the condition was considered unusual, but its importance has only recently been fully appreciated.

Since the subject of bone tumors is at present in a state of flux, an extensive reference to the literature will not be made in this report. It is felt that our purpose will be best served by the mere recording of this case in detail, so that the report may be available for the purpose of study and comparison of the condition with other similar lesions.

The condition of malignant chondroma is referred to briefly by most of the standard authorities. Bland-Sutton [1] refers to the possibility of chondrifying sarcoma, and both McFarland [2] and McCallum [3] refer to the subject in their textbooks. Ewing [4] says that the malignant quality of chondrosarcomas is often out of proportion to their cellular quality. He says that both clinical and histologic features must be taken into consideration in the diagnosis of chondrosarcoma, as the histologic structure does not always suggest malignancy. Bloodgood [5] asserts that the only chondromas he has seen cured have been those in which the involved bone was removed by resection or amputation without the exposure of tumor tissue.

In the case recorded here, there was never at any time anything that suggested malignancy in the histologic picture.

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1. Sutton, R. B.: Keen's Surgery **1**:750.

2. McFarland, Joseph: Surgical Pathology, Philadelphia, P. Blakiston's Son & Company, 1924, p. 243.

3. McCallum, W. G.: Textbook of Pathology, Ed. 2, Philadelphia, W. B. Saunders Company, 1921, pp. 943-944.

4. Ewing: Neoplastic Diseases, Ed. 2, Philadelphia, W. B. Saunders Company, 1922, p. 185.

5. Bloodgood, J. C., quoted by McFarland (Footnote 2).

REPORT OF CASE

History.—J. F., a widower, white, aged 48, consulted one of us Dec. 7, 1909, on account of a swelling of the left thigh, and severe pain in the left knee. Twenty-seven or twenty-eight years before, the patient had been squeezed between a cart and a stone wall, the left thigh receiving most of the pressure. Following this experience, he was free from symptoms until one year before he sought advice, that is, for twenty-seven years, when he began to experience pain in the left knee. At first, the pain was felt only at the end of a hard day's work; later, it became continuous, although it was worse at night. On his admission to the Pennsylvania Hospital the pain was located about the knee and over the anterior surface of the thigh. Ten days previously, he had been told by another surgeon, after roentgen-ray studies had been made, that the condition was inoperable. The patient's past medical history and family history were entirely negative. He had seven childrn, all of whom were living and well. He had worked for the previous fourteen years as a packer and shipper in a hardware store, but he could not remember having received any injuries to his leg during that time.

Examination.—The patient presented the appearance of a well-developed, middle-aged white man. The lower half of the left thigh was enlarged, measuring 1 inch (2.5 cm.) more in circumference than the right. From the posterior surface of the femur, 6 inches (15.2 cm.) below the trochanter, a lemon-sized, hard, immovable tumor projected. It was painless, but pressure applied to it caused pain to be felt in the knee. Roentgenograms revealed the tumor clearly, and also showed a fusiform enlargement of the lower half of the femur. Other laboratory studies do not seem to have been made at that time.

First Operation.—The first operation was performed December 15. The mass was exposed by splitting the muscles; the actual tumor, about the size of a walnut and of a cartilaginous consistency, was removed by chiseling through the bony pedicle. It appeared to have perforated the cortex of the femur.

The pathologic report made by Dr. W. T. Longcope, December 31, revealed that the specimen consisted of an irregular knobby mass about the size of a walnut. It was gray and cartilaginous in appearance but covered with fibrous tags, and the cut section looked like a mass of rolled up, icy, translucent membrane about 0.5 cm. thick, between which was a granular material of the same icy character. The mass was firm, but cut readily except for the small bony pedicle about 1 cm. in diameter. Numerous sections from all parts of the tumor showed about the same appearance. It was composed of cartilage, surrounded by more or less dense connective tissue, and the cartilage was arranged in lobules, between which there was connective tissue and bone. The separating trabeculae were rather vascular. The cartilage showed in places vacuolization and, occasionally, actual degeneration. There were very few cells. The case was diagnosed as one of osteochondroma.

December 25, the patient was discharged from the hospital free from symptoms, the wound having healed by first intention. While he was at home he had another roentgen-ray picture taken, which showed merely the fusiform enlargement of the femur previously noted.

The pain gradually returned, and by Feb. 1, 1910, it was so severe that he again entered the Pennsylvania Hospital, and was admitted to Dr. LeConte's service.

Second Operation.—One of us opened the medullary cavity and with a curet removed a quantity of firm cartilaginous material exactly resembling the specimen which had been removed at the first operation. A clinical diagnosis of sarcoma was made, but as no permission to amputate was given the wound was drained.

The pathologic report of Dr. Longcope revealed that the specimen consisted of a number of pieces of soft cartilaginous tissue, and bone. Micro-

Fig. 1.—Femur sawed open: *A*, anterior view, showing distortion of normal anatomy and angular deformity of healed fracture with tumor mass at site of fracture just below trochanter; enlargement of lower half of shaft, as well as erosion of head of bone and ligamentum teres may be noted; *B*, posterior view, showing medullary canal filled with tumor tissue. Just below the middle of the shaft is the hole, still filled with cartilage, through which the pedicle of the original tumor projected.

scopically, the section showed areas of cartilage with rather irregular cell spaces and cells contracted within them. In one place near the margin were strand-like masses of young connective tissue, with many young spindle and triangular fibroblastic cells. There were great masses of red blood cells and many young vessels. The case was diagnosed as one of enchondroma.

Dr. Bloodgood saw the patient at this time in consultation, and also examined the specimen removed and sections of this tissue. He agreed with Dr. Longcope's diagnosis, and said that it was undoubtedly a benign condition, and he advised against amputation.

February 5, the wound of the first operation reopened and began to discharge a thin, gliary colorless fluid like joint fluid. March 5, the discharge from both wounds was identical and the culture taken revealed the presence of streptococci.

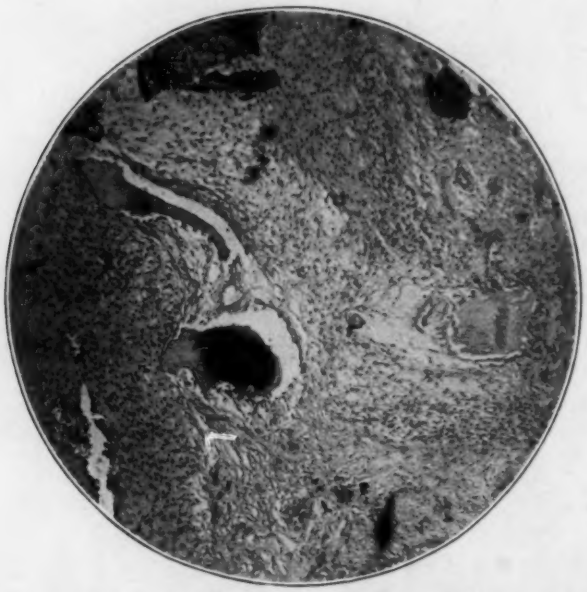

Fig. 2.—Tumor tissue (low power photomicrograph), showing atypical hyaline cartilage varying somewhat in its structure.

Third Operation.—On May 7, an enlarged inguinal gland was excised. Dr. Longcope reported that it merely showed chronic adenitis, and that there were no signs of tumor tissue.

Fourth Operation.—May 7, the fourth operation was performed because of the two sinuses that refused to heal. One of us exposed the entire shaft of the femur. The periosteum was found to be thickened, and the surface of the cortex was roughened by the growth of the tumor between the cortex and the periosteum. The entire narrow cavity was found to be filled with the same cartilaginous material, which had reformed since the third operation. The whole medullary cavity was emptied, and its walls were thoroughly curetted. A small hole was found in the middle third of the cortex, through which the pedicle of the original tumor had passed (Fig. 1, *B*), furnishing proof of its medullary origin.

Dr. Longcope reported that the specimen consisted principally of two large cylindrical masses of tissue forming a complete cast of the medullary canal of the femur. The masses had a white semitranslucent, opalescent appearance, and the tissue seemed to be formed of a great number of parallel columns of villi. It broke apart along the lines of these columns. In the center of the mass was an area of soft, yellowish material. A small piece of periosteum was soft, and on section showed a pale brown, gelatinous substance, coursed by several gray-white strands. Sections from the portion of the growth removed from the medulla of the femur, seen under the microscope, were composed almost exclusively of cartilage. There were a few clefts in the cartilage containing red blood cells. The tissue had a slightly reticulated appearance, with large

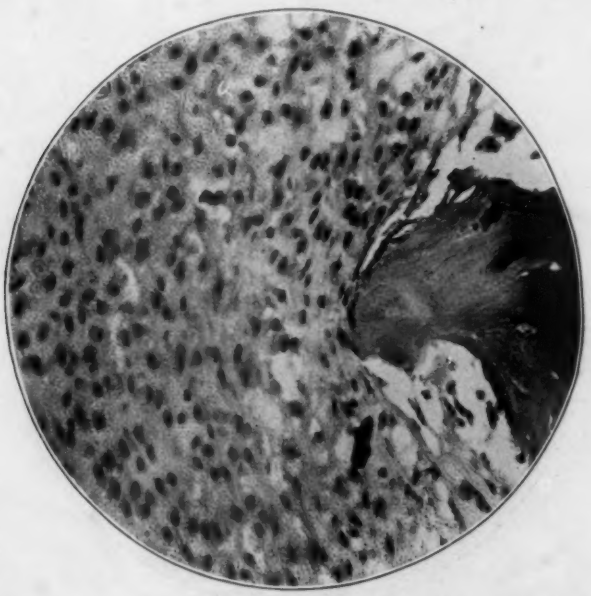

Fig. 3.—Tumor tissue (high power photomicrograph), showing more clearly the cellular structure.

and irregular cells. The protoplasm was vacuolated; the nuclei were small, shrunken and often pyknotic. The cell spaces were scanty. The section from the periosteum showed no cartilage. It was composed of voluntary muscles showing extensive inflammation, with degeneration of the muscle fibers. This tissue was infiltrated with small, round cells, plasma cells, and epithelioid cells. In places there were large collections of lymphoid cells showing germinal centers. The case was diagnosed as enchondroma, with chronic inflammation of the muscle covering the periosteum.

On June 18, 1910, the patient fell from his wheel chair and fractured his left femur just below the trochanter. By August 10, the fracture had firmly united; the sinuses were still open and discharging the same clear gliary fluid. By September 10, the wounds had closed, and the roentgen ray showed that the fracture had healed with marked angular deformity. There was an indefinite mass, not callous, about the fracture. On Nov. 8, 1910, both sinuses had

reopened and were discharging the same clear fluid as before. The mass about the fracture had distinctly increased in size, and a hip joint amputation was advised.

Fifth Operation.—Nov. 26, 1910, one of us disarticulated the left femur at the hip joint. The tumor was found to involve the entire neck, trochanters, and the site of fracture; the characteristic gliary fluid was escaping from the open medullary cavity. When the head of the bone was delivered, it was found that the ligamentum teres was destroyed, probably by the tumor, and that the acetabulum was eroded in several places.

The pathologic report of Dr. Longcope revealed the fact that the upper end of the femur (the upper half of which had been sawn through longitudinally) (Fig. 1) including the trochanters and the greater part of the neck was included

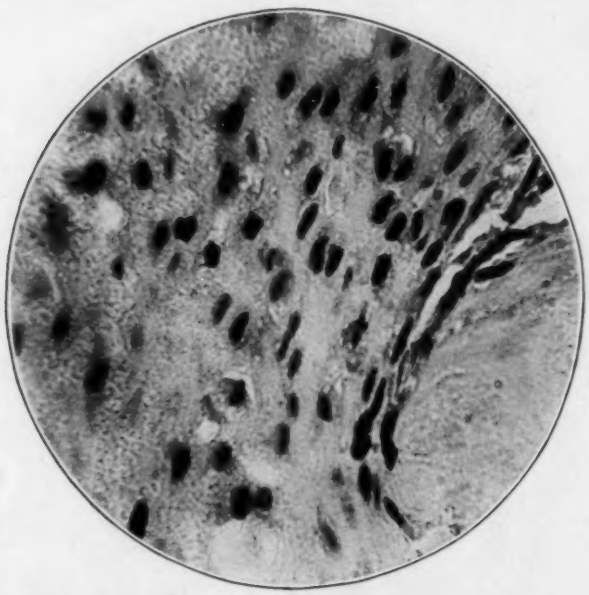

Fig. 4.—Tumor tissue (still higher power photomicrograph); the area differs little, if at all, from normal cartilage in appearance.

in a hard nodular mass 8 by 10 cm. Small areas of this mass were of cartilaginous consistency; elsewhere, it was of a bony hardness. The sectioned surface showed hard and spongy bone with a few softer areas. Just below the center of the shaft posteriorly was a round hole, 2 cm. in diameter. This was filled with soft spongy material, continuous with a mass of similar material described above, which filled the greater part of the medullary cavity. The lower portion of the shaft, unopened, was considerably thickened.

Sections from the spongy mass of the shaft showed a cellular structure in which were small masses of cartilage with a little calcification. These were imperfectly surrounded by rather heavy strands of fibrous tissue. The cartilage was of the hyalin variety (Fig. 2), and the matrix was rather abundant; the cells were mostly round, enclosed in clear spaces, and varied considerably in size and in staining qualities. Some were pale, others hyperchromatic; an occasional double nucleus was noted. The arrangement of the cells was

entirely disorderly. The greater part of the field, however, was occupied by fairly large, round or oval nuclei, without apparent individual cell body. These were dotted over a pink staining matrix, mostly homogenous, but in part showing a fibrillar structure. These cells varied much in size and in staining properties. Mitotic figures were not seen. This structure blended gradually with some of the areas of cartilage, and also, in other places, with the fibrous tissue, the nuclei gradually assuming a spindle shape. A number of thin-walled blood vessels were seen. A section taken from the mass at the head of the bone showed a similar structure, with, however, a greater portion of the cellular and fibrous tissue and fewer blood vessels. A decalcified section taken from the hard part of the tumor showed a formation of true bone, with haversian system. The case was diagnosed as osteochondrosarcoma.

Following the amputation, the patient steadily recovered. For about a month he complained of the same pain in his knee as before the amputation, but then it disappeared. For a month he was given Coley's fluid, but it caused him so much distress that he refused to have it continued. He was discharged March 1, 1911, with the wound healed except for a very small sinus which was discharging the usual colorless, gliary fluid. The case was followed in the outpatient department and the patient received regular roentgen-ray treatment.

Sept. 3, 1912, the patient was readmitted complaining of a large growth at the site of amputation, and severe pains, requiring large doses of morphin. The mass at the site of the stump measured 33.5 cm. in diameter; on it was a large roentgen-ray burn.

Sixth Operation.—Nov. 16, 1922, one of us attempted to ligate the femoral artery in Scarpa's triangle on account of visible pulsation, but the tissues were too friable. The external iliac artery was ligated instead. The wound refused to heal, and the roentgen-ray burn also increased in size. By December 5, it was apparent that the stump was growing larger. Between December 19 and December 23, he had a number of profuse hemorrhages from the still unhealed wound in Scarpa's triangle, from the last of which he died.

There was no necropsy, but after death a piece of tissue was removed from the mass on the stump. Dr. Longcope reported that this tissue was pale and of a cartilaginous appearance, softer in consistency than normal.

Microscopically, fibrous tissue was seen at the site of infection and some granulation tissue and there were also occasional giant cells. One area showed some epithelial cells with brown pigmentation among some spindle cells and some gray staining material. Another section showed fibrous tissue surrounding some blue staining, fibrillar material that had vacules and resembled cartilage. Other areas showed fibrous tissue occupied by small round cells in focal collections and areas of congestion. Cartilage cells showing mitotic figures were present in areas. The case was diagnosed as enchondroma.

EXPERIMENTAL END-TO-END ANASTOMOSES OF THE COLON*

AN ANATOMIC STUDY

FERDINAND C. LEE

BALTIMORE

During the last few years the consideration of aseptic methods for the anastomosing of the large bowel has received a new impetus. Undoubtedly, the late Dr. W. S. Halsted was chiefly responsible for the eagerness and enthusiasm with which the problem was attacked in this country, and it is due directly to his influence that numerous ingenious methods have been devised. However, one striking feature of all the reports on the various procedures employed is that the anatomic control of the method has received either no attention or, at best, only scant attention. As a rule, the investigators have been satisfied with their method when they have found that their animals survived the operation. It is the purpose of this report to bring together some of the anatomic data bearing on the process of the healing of anastomoses of the large bowel in general, rather than to detail the results of one method of anastomosis in particular.

OPERATIVE PROCEDURE

The method of aseptic anastomosis of the large bowel employed in all but one of these experiments has been reported elsewhere;[1] the one operation not done by this method was performed after the manner described by Horine,[2] and will be discussed later. The special instrument used consisted essentially of a hollow metal tube through one end of which the suture temporarily occluding the bowel was threaded. Later, this suture was severed by means of a very small chisel, which was thrust into the lumen of the metal cylinder. The two ends of the intestine were united by three silk stay sutures and by a single row of closely spaced Halsted silk mattress stitches which encircled the bowel. In certain cases, the muscular wall of the bowel was cut first with the scalpel around its entire circumference until the submucosa was reached; in the majority of cases, however, the same purpose was accomplished by the ligating thread, which was drawn so tightly that the muscular coat was cut by the ligature. One could easily feel the thread sever the

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*From the Anatomical Laboratory of Johns Hopkins University Medical Department.

1. Lee, F. C.: Eine neue Methode zur aseptischen End-zu-endanastomose des Dickdarmes. Deutsch. Ztschr. f. Chir. **179**:402, 1923.

2. Horine, C. F.: Aseptic Technique for Resection of Intestine, Ann. Surg. **76**:745 (Dec.) 1922.

musculature. Proper ligation of the bowel was considered an important step in the technic, and it was found that linen thread was the most suitable material.

All the operations were performed under ether anesthesia on nine dogs that varied in weights from 18 to 26 pounds (8 to 12 kg.); only one dog weighed as little as 10 pounds (5 kg.). In these nine dogs, twelve anastomoses of the colon were made. One of the dogs had two anastomoses made at the first operation, while in two other dogs the second anastomosis was made several months after the first one. The animals were kept alive for various periods of time in order to secure anastomoses of various ages. In no case did peritonitis or any other complication determine the time of killing. At the time of killing, they were first put under the influence of ether, the abdomen was opened and the operative sites carefully inspected. In four of the animals, injections of Berlin blue were made into the tissues at the site of the anastomosis in the hope of filling lymph vessels. In all cases, a blood vascular injection with India ink was made. After the injection, the entire segment of the bowel was fixed in 10 per cent. liquor formaldehydi for one hour; it was then cut open opposite the mesenteric attachment, pinned out on cork and put back into the same fixative. Photographs of the gross specimens were taken after a week or ten days, and then blocks of the tissue were taken for the preparation of celloidin sections. The sections, cut from 10 to 15 microns thick, were stained in hematoxylin and eosin, iron hematoxylin and mucicarmine, Mallory's connective tissue stain, Weigert's elastic tissue stain, or preferably in a triple stain which gave very attractive preparations and consisted of passing the section successively through iron hematoxylin, mucicarmine and van Gieson's connective tissue stain. Furthermore, thin blocks of the formaldehyd fixed tissue were cleared by the Spalteholz method in order to study the vascular distribution at the anastomosis. In brief, material was obtained which showed anastomosis of the following ages: 4, 7 (two specimens), 16, 30 (two specimens), 86, 104, 133, 177, 186, and 213 days.

OBSERVATIONS

General.—The number and extent of the adhesions at the anastomosis were inversely proportional to the care with which the tissues were handled at the time of operation. As a rule, that part of the bowel opposite the mesenteric attachment was most free from adhesions, while the portion near the mesentery of the resected piece had adhesions most frequently. In those operations that came early in the series and took more time to perform, adhesions were more frequently met with. However, as proficiency in the technic was acquired, the adhesions

became less and less in number and degree, in spite of the fact that at that time a double anastomosis was attempted. In those animals in which the anastomosis had been made for only four to seven days, neighboring loops of bowel were attached to the colon at the place of operation, but their attachment was very slight, and separation was easily accomplished. The most satisfactory specimen so far as adhesions are concerned was represented by Figure 1, which shows the outer surface of the large bowel with its two anastomoses completed at the same operation, each being 177 days old. At *B*, the musculature was cut with the scalpel down to the submucosa; while at *A*, the musculature was severed by the ligating thread. The two scars representing the lines of union are definitely visible, and the cut end of the mesentery can also be distinguished readily. It will be seen that the scar cor-

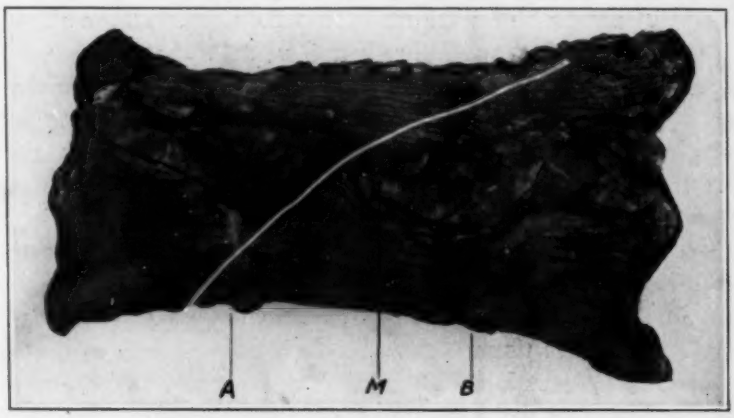

Fig. 1 (Dog A 8).—External view of large bowel of a dog, which has been opened opposite its mesenteric attachment, *M*; the two anastomoses at *A* and *B*, each 177 days old, with absence of adhesions may be noted. At *A*, the tunica muscularis was severed by the ligating thread, while at *B* it was cut with the scalpel; the scar is more dense at *A*; × 2/3.

responding to anastomosis *B* is flatter, smoother and less easily seen than is the scar of anastomosis *A*, which is more puckered and elevated. Palpation revealed in the fresh state that the line of anastomosis of *B* was not as broad, thick, or indurated as that of *A*, and that the inference was that the union at *B* was better than at *A*. Both inspection and palpation showed that there was some constriction, although extremely slight, at both *A* and *B*, yet an appreciable difference between the two was not noted. After the bowel had been opened opposite its mesenteric attachment, it was seen that practically no constriction occurred at either *A* or *B*, and that the degree of constriction was about the same for the two (Figs. 2 and 3).

In general, constriction of the lumen of the bowel varied inversely with the age of the anastomosis. Anastomoses that were four days old showed more obstruction to the lumen than those seven days old, while the one of sixteen days' duration had less constriction than those of seven days' duration.

Another factor influencing constriction was the size of the animal. The larger the dog the more easily was the sewing done, and the less was the ratio between the tissue turned into the lumen and the cross section of the lumen itself; as a natural result, the less was the con-

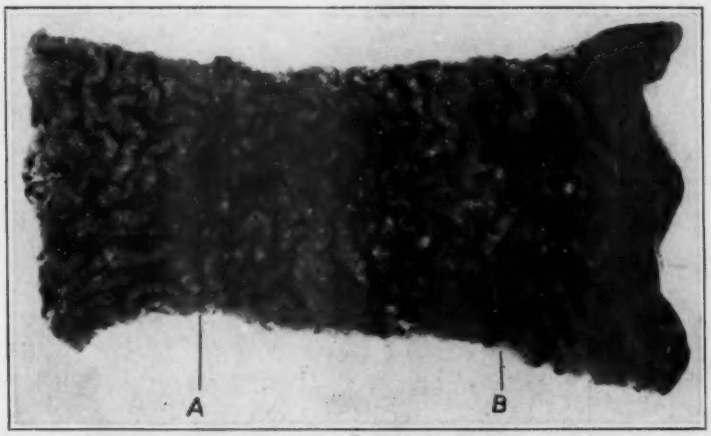

Fig. 2.—Mucosal surface (same specimen as Figure 1) Showing the two anastomoses at *A* and *B*, with slightly more constriction at *A*; × 2/3.

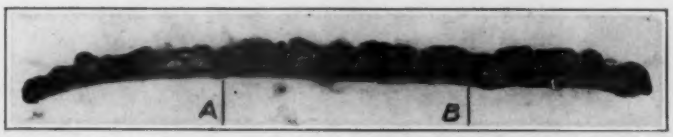

Fig. 3.—Section of intestine (same specimen as Figure 1), with the two anastomoses at *A* and *B*; absence of a diaphragmatic constriction at these two places as well as uniformity of the muscle layers. At *B* the transition is slightly better than at *A*; × 2/3.

striction. In this series, the oldest anastomosis was of 213 days' duration; this specimen would be expected to present, at least from the point of time, the best anatomic result and the least constriction. But this anastomosis was performed on a small dog that weighed only ten pounds (5 kg.), and showed a constriction of about 15 per cent. Ordinarily, the amount of obstruction, which was about 60 per cent. of the lumen in the anastomosis of four days' duration, gradually decreased to 10 per cent. in the cases of more than thirty days' duration.

Changes in the Mucosa.—The study of the changes in the mucosa as a result of the anastomoses has been interesting in several particulars. In the first place, in all anastomoses thirty days old or more, the mucosa had completely healed. The one exception to this statement was an anastomosis of thirty days' duration, which showed the very apex of a small fibrous projection still unepithelialized. To offset this case, however, a complete epithelial lining was secured as early as the sixteenth day (Fig. 4).

Fig. 4 (Dog A 7).—An anastomosis of 16 days: a single layer of epithelium, which has covered the defect in the mucosa, also shows the formation of crypts; the area marked by the letter *F* has been photographed with a larger magnification (Fig. 8). The proximity of the young epithelium to the circular muscle layer is seen. *G* marks the site of a stitch, with foreign body giant cells and an acute inflammatory reaction extending to the lumen of the bowel, as well as to the peritoneum; × 8.

The process of epithelialization consisted in the proliferation of epithelial cells from the normal, intact mucosa over the intervening infected and necrotic fresh granulation tissue, to establish a connection with a similar epithelial sheet coming from the opposite side. The cells of the vanguard were in a single layer, flat, markedly young and embryonic in appearance (Fig. 5). When an obstruction was encoun-

tered, such as a hair or the egg of an intestinal parasite, then the head of the column doubled back on itself for a distance of several cells, the individual cells became more cuboidal and the nucleus more centrally placed. Ordinarily, the column followed the path of least resistance, which was on the surface of the granulating tissue; but sometimes the advancing cells would find their way into superficial parts of the loose granulation tissue. In no case was the free border of the cells in direct contact with any foreign object; a clear zone always intervened. A clear area was also seen usually at the very apex of the advancing column, and the impression was gained that this clear area represented, at least in part, material secreted by the young epithelial cells, and that this material was conducive to further proliferation in that in the first place it formed a protective layer at the free border, and in the second

Fig. 5 (Dog A 11).—Material from an anastomosis of 7 days showing the type of the youngest epithelium, *E*: the free surface of these cells has a clear zone which underlies an exudate; the cells are flat and embryonic in appearance, merging with columnar epithelium, with its superposition of nuclei accounting for the dark color; × 190.

place it functioned as a matrix into which the advancing pseudopodia projected.

Numerous areas were seen in which the epithelial column was covered, except for the clear zone, with exudate and débris, and it seemed as if the epithelial cells were forcing their way into loose infected material. Again, localized islands of young epithelial cells were seen completely surrounded as far as the individual section was concerned, but showing nevertheless marked proliferation. Probably these isolated epithelial areas were connected with the main epithelial layer by means of irregular and tortuous projections, which followed the crevices of the ulcerated area; or they were strictly isolated but receiving enough nourishment for proliferation.

In several sections, it was seen that the column of epithelial cells came in contact with a bit of thick silk thread and that the naturally narrow band of cells became extremely flat, with the first two or three cells as flat as the pavement epithelium. Nevertheless, although the cells were attenuated, they still had the clear zone previously mentioned.

The cell at the very apex of the advancing column showed a regular outline with the exception of irregular projections resembling pseudopodia, which were extended in the direction of further advance. The cytoplasm had an indifferent, uniform, ground-glass appearance, suggested by the presence of numerous small, clear granules. The nucleus, invariably large and vesicular, occupied the greater part of the cell; occasionally, it showed a darker stain because of the superposition of other nuclei with their chromatin material. The entire cell reflected in appearance a young, embryonic structure with marked potential properties of proliferation.

The character of the epithelial cells changed with respect to their peripheral or central position.[3] The cells gradually lost their flat appearance and became cuboidal. At the same time, the free border of the cell showed a thickening, which resolved itself into a layer of cilia that were short and thick, and had their presence accentuated by a thin application of red stained mucus which aided in their identification. The cytoplasm showed a condensation at the apical part of the cell, with a vacuolar appearance at the base.

More centrally, the cells showed a very marked nuclear proliferation, and at the same time became more cylindrical. The free border now showed the curious ciliary margin more definitely, with each cilia not only distinct and long but showing near its extremity a small knob-like enlargement which was particularly prominent when it was surrounded by a small amount of mucus (Fig. 6). In some sections, a surface view of the cilia was obtained, and in such a preparation the individual nature of each cilium was evident from the regularly stippled appearance of the gland lumen. On cells more centrally placed, the enlargements at the end of the cilia appeared more fused and represented a limiting layer, which blended with a corresponding structure of the normal epithelium. The cytoplasm of these young cylindrical cells was granular throughout, but chiefly towards the apex of the cell; in certain cases in which the cells formed part of the bottom of a crypt, the cytoplasm was condensed near the base with the apex more vacuolated. In many cases, the base of the cells was in contact with large vacuoles which actually separated the cells from their young, underlying, basement membrane of fibroblasts and did not form part of the cytoplasm.

3. For descriptive purposes in this article the term "peripheral" when used in connection with epithelialization will mean toward the point of epithelial advance, while "central" will refer to the opposite region.

The manner in which the goblet cells made their appearance was interesting. These cells were never found when the epithelium was flat, and, although they infrequently appeared in the early stages of development when the epithelium was cuboidal, it was only when the epithelium became definitely columnar that the mucus was formed. Figure 7 indicates how the mucus gradually became differentiated in the distal portion of the cell. This material appeared first at the apex of the cell as a small indefinite mass that took the mucicarmine stain very lightly. More centrally, the epithelial cells showed a definite spherical segregation of mucus situated at the free border of the cell and occupying its entire width. Still further centrally, this mass occupied more of the distal part of the cell and projected a blunt process towards the nucleus. The last stage was found in cells that were

Fig. 6 (Dog A 6).—From an anastomosis of 98 days, showing the peculiar enlargements at the end of the cilia, *C*. These cells were situated near the middle of a gland.

typical of the goblet variety with the exception, however, that the cells were smaller than the true goblet cells and that the amount of mucus was correspondingly less.

The young goblet cells were found first singly or in groups of two; and as the examination extended centrally, their aggregated number increased until they were as numerous as in the normal adult mucosa. As these cells became larger they showed a more granular appearance, and even exhibited a mesh in which the mucus seemed to be supported.

The columnar epithelium also showed instances in which the nuclei were very near to, and even on, the free surface of the cells. Again, small, black-staining granules were often seen on the free surface, and the impression was gained that these granules were remnants of nuclear fragmentation. Furthermore, it seemed as if these isolated cells, which

were not polymorphonuclear leukocytes as indicated by their nuclei, had taken a course extending from the base to the apex of the columnar cells, and that they were eventually liberated or possibly forced out at the free surface. Small cells with a dense small nucleus were seen at the base of the columnar cells; at times, the nuclear material was bilobed or divided. The exact classification of these cells could not be made.

Evidence was also obtained regarding the formation of the crypts. As early as the seventh day after operation, a localized proliferation of cells was observed at the basal portion of the young epithelium, in such a manner that the cell mass protruded into the underlying connective tissue stroma. The individual cells making up this mass were as young and embryonic in appearance as those at the very apex of the advancing epithelium; no mucus was formed by them. In the specimen obtained

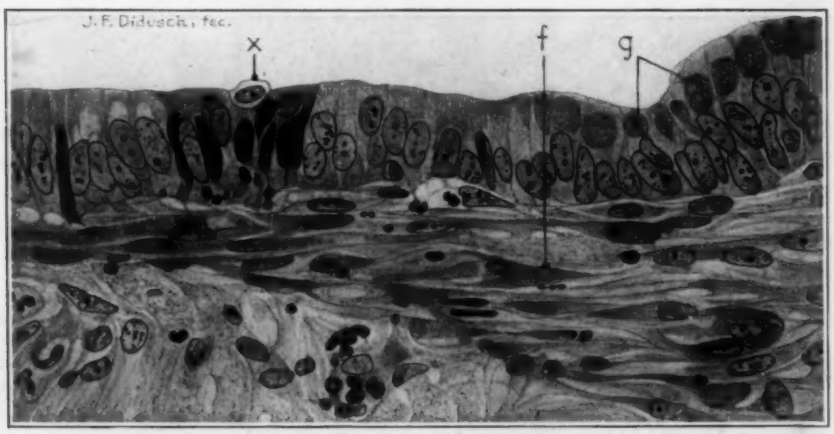

Fig. 7 (Dog A 11).—The gradual appearance of the goblet cells, *G*. The left of the illustration is practically a continuation to the right of Figure 5: the cell, *X*, lying superficially on the mucosa, is an example of the cells seen throughout the thickness of the mucous layer. The layer of fibroblasts, *F*, immediately underlying the mucosa, becomes progressively narrow as it approaches the apex of the advancing epithelial cells.

sixteen days after operation, not only the numerous cell masses just described but also the beginnings of typical crypts (Fig. 8) were seen. The crypts did not extend deeply into the underlying connective tissue, the largest crypt being only twice the length of the columnar epithelial cells at the mouth of the gland. The cells of the crypts were more cuboidal than the neighboring columnar cells on the free surface. They showed marked evidence of proliferation, with vesicular nuclei and many mitotic figures. However, certain of these cells had differentiated to the extent that they were supplying the typical appearance of the normal crypts by being definite small goblet cells; although their number was few,

Fig. 8 (Dog A 7).—A magnification of area *F* in Figure 4, showing the early formation of the crypts; the cells on the surface are columnar with only a trace of mucus; a goblet cell of good size, *H*, has however, formed in a crypt, which is resting on a layer of young connective tissue; × 525.

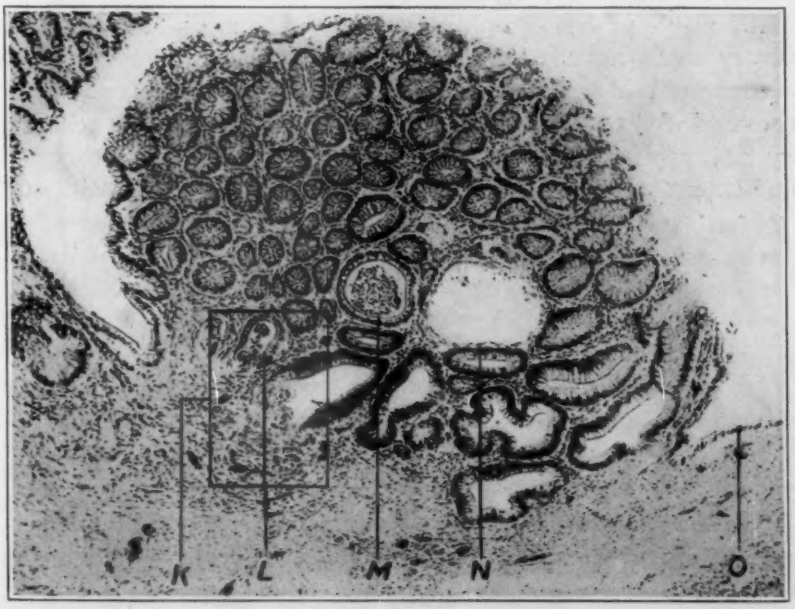

Fig. 9 (Dog A 11).—An anastomosis of seven days; cysts in varying sizes *L*, *M*, and *N* may be seen; some of the epithelium lining of *N* still has large cilia; the glands below the cysts are large and irregular. *O* shows a column of epithelium advancing to join the epithelium of Figure 5, and *K* represents an area magnified in Figure 10; × 70.

it was greater than the incidence in the surface epithelium. In an anastomosis thirty days old, the crypts had so completely formed, and their appearance was so like the normal crypts, that the site of anastomosis could not be identified by inspection of the mucosa alone.

The formation of cysts of the mucosa at the site of young anastomoses was invariable. These cysts were as a rule small; none was observed having a diameter as great as the length of a crypt, while the majority were never greater in cross-section than one-third the length of the gland. In Figure 9, numerous cysts of various sizes are seen. They were characterized not only by their large lumen but also by the detritus, which consisted mainly of mucus and free cells, reminding one of those cells found on the free surface of young columnar epithelium; in no case were white blood cells seen. In large cysts, the detritus showed fewer cellular elements and, as a rule, less mucus; however, in the anastomosis of 133 days' duration in which there was the largest cyst, the content was practically all mucus. The epithelial lining of these spaces had a height that varied inversely with the size of the cysts. In the smaller cysts, the epithelium was more cuboidal and contained numerous goblet cells which were also shorter than normal; in the larger structures, the epithelium was flat, with practically no goblet cells, although it did have cilia of normal size.

The glands at the site of anastomosis were much larger than the ordinary ones, with the individual cells longer, and with much greater evidences of cell proliferation. Moreover, these large, young glands showed marked cell division in certain regions in which the cells were very embryonic in character and where they invaded the connective tissue stroma in a lawless cancer-like manner (Fig. 10). Finally, small islands of very young epithelial cells, which were usually cross-sections of the base of incomplete crypts and which probably arose from a nucleus of a few cells taken from the base of normal glands at the time of operation, were also observed at the site of anastomosis.

Underneath the peripheral part of the advancing epithelium a layer of fibroblast also proceeded. This layer became successively thinner as the periphery was reached, and did not underlie the first five to ten cells. On the one side, it was flanked by the epithelium, and on the other side it was constantly exposed to an infected area (Fig. 7).

Muscularis Mucosae.—The muscularis mucosae proved to be the surest index for determining the site of previous operation. In no case was it found to be a complete, normal layer, for it always showed an abundance of scar tissue even though the muscle had been given, in one case, seven months to effect a complete union. Normally, for this region of the dog's bowel, the muscularis mucosae reflects the arrangement of the tunica muscularis in that it has two divisions, an inner circular, and an

outer longitudinal coat. In the healing process, the two divisions not only lost their identity but joined imperfectly with the opposite muscle layers. An abundance of scar tissue in contradistinction to plain muscle was always found, even in the one case that went for seven months. Weigert's elastic tissue stain showed a large amount of elastic tissue formed at the site of union, which contributed largely to the strengthening of the intestinal wall at this point.

Fig. 10.—The area *K* of Figure 10 magnified; the marked proliferation of only part of the gland is shown; the young cells are very embryonic in appearance and are arranged mainly to form glands, as indicated at *Q*. These young structures have no goblet cells; the dense black areas, like the one lettered *F*, are sections of blood vessels filled with India ink; × 290.

The muscularis mucosae was definitely absent in those regions where solitary lymph follicles were in intimate contact with the mucosa. The follicles were frequently found near the anastomosis and often allowed crypts of Lieberkühn to dip into them to a marked extent. In these cases, the cells of the epithelium of the crypts appeared young and small, with no evidence of goblet cell formation.

Submucosa.—The submucosa, with its newly formed granulation tissue, showed the greatest activity in the young anastomoses. However, in the old anastomoses it was present to a degree far less than normal, and in many cases it was almost absent. It contained a large amount of very vascular, densely packed scar tissue as well as a small amount of elastic tissue. In practically all the older cases, the fibrous tissue had contracted down to such a degree that the base of the crypts was almost on the circular muscle layer; in one case in which the muscular coats had not been approximated accurately, the scar tissue, which was identified chiefly with the submucosa, formed the only layer between the mucosa and the peritoneum. Since the muscle layer had not united across the anastomosis in the latter instance, the natural limits of the submucosa were not given, and the fate of the submucosa became inseparably linked with the fibrous tissue arising both from the muscle layers and from the subserous connective tissue.

Tunica Muscularis.—The two muscular coats, the outer longitudinal and the inner circular, showed no characteristic differences in their manner of healing. In the young anastomoses, the muscles were in apposition, with their cut ends turned towards the lumen of the bowel. However, when the mattress stitch had not taken firm hold in the submucosa but had included only muscle, a separation occurred which, in one case of seven days' duration, was about half the thickness of the normal intestinal wall near that point. The severed edges of the muscle showed definite evidence of slight regeneration, which was less marked with the increasing age of the anastomosis. In some cases, the musculature was turned in more from one side than from the other; in these cases, the outer longitudinal layer reached the submucosa and united with the inner, circular layer of the opposite side. In those instances, however, in which the same amount of musculature was turned in from either side, and the respective muscle layers were in apposition, healing took place so well that the line of union was not obvious (Fig. 11). Then, only a very small amount of fibrous connective tissue formed at the anastomoses, making the contracture on this line small, and preserving a lumen of the bowel which was less than 10 per cent. smaller than the normal neighboring bowel.

Between its narrow annular segments, the circular muscle layer showed extravasations of blood near the line of anastomosis. These extravasations were never large, nor did they extend laterally for a distance greater than the width of the tunica muscularis itself. They were most marked in the anastomosis of four days' standing, while in the speciments of seven days' duration it was impossible to find any extravasations. Similarly, in the longitudinal muscle layer, free blood was also found; but it was less in amount and distribution than that observed in the circular muscle.

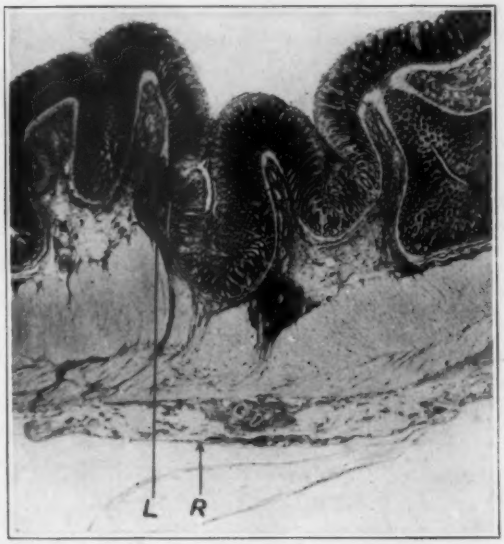

Fig. 11 (Dog A 6).—An anastomosis of 186 days, with the line of union marked by *R*: the mucosa has healed perfectly. The muscularis mucosa is deficient at *R*, as well as at *L* where a solitary lymph follicle reaches the mucosa; the submucosa is scant. The circular and longtiudinal muscle layers are in communication across the anastomosis; the tunica serosa is thickened and has a peritoneal tag; × 8.

Fig. 12 (Dog A 7).—An anastomosis at *C*, which is 86 days old, and another at *D*, which was subsequently performed proximally, giving an anastomosis of 16 days; the inturning at *D* with a gap between the muscle layers which is filled by young connective tissue. Obviously the stitch here did not hold as well as the one shown in Figure 4, which was taken from adjoining material. The great difference in the circular muscle layer (*cm*) between the bowel proximal and distal to the old anastomosis (*C*) is striking; × 2/3.

Inspection of the longitudinal section of the anastomoses showed that the muscle layers often varied in thickness in the same specimens; particularly was this true of the circular layer. Figure 12 shows a strip of bowel, having one anastomosis at *C* which was 86 days old, and another at *D* which was 16 days of age. Immediately on top of the uniform white band, which is the longitudinal muscle layer, was seen the circular muscle layer which extended as a broad dark band to the right of *C* with an interruption at *D*, whereas to the left of *C* it was comparatively narrow and normal in appearance. In Figure 3, however, which also shows two anastomoses, but which are of the same age, one at *A*, and another at *B*, the circular muscle layer is of the same thickness throughout.

Serosa.—The conditions of the serous membrane reflected the operative technic very accurately. Whenever the peritoneum was markedly injured, adhesions formed connecting the line of juncture with the neighboring bowel, or, as was more usual, with the omentum. In all cases, the subserous tissue was definitely increased in amount even in such a specimen as Figure 1 illustrates, in which no adhesions were found at either anastomosis. This thickening, which extended for a distance equal to the thickness of the intestine and reached its maximum opposite the line of anastomosis, was composed mainly of very vascular fatty connective tissue. In some cases, the peritoneum was reflected over fatty areolar tissue, forming a structure resembling an epiploic appendix. In other instances, the subserous connective tissue layer was markedly thickened at regions not on but adjoining the line of anastomosis; occasionally, omental adhesions also developed in these localities, leaving the line of intestinal juncture free.

The Infected Area.—Obviously, one of the points of great interest in this investigation was the study of the rôle that the infection played in the healing process. In the young anastomoses, the epithelium had not closed over the raw, intervening, ulcerated area, which chiefly had as its base the submucous layer, and in this infected area was seen young granulation tisssue, which had enmeshed material that was normally part of the contents of a dog's large intestine. In the superficial layers were found countless amebas, numerous eggs of parasites, hair and undigested bits of food. Free mucus was also mixed with the granulation tissue and, although it was situated mainly in the superficial parts of the ulcerated area, it was also observed in the deeper portions of the submucosa. In the deeper portions of this granulation tissue which undermined in the submucosa the muscularis mucosae, the amebas and the eggs were no longer present, but the hair still persisted. In fact, in the anastomosis of ninety-eight days' standing, bits of hair were still found in the scar tissue near the serosa. The presence of large

numbers of polymorphonuclear cells testified to the infectious process taking place near the bowel lumen; their presence opposite the muscle layers and even at the peritoneum showed that the deeper layers of the bowel were also coping with infection. In the anastomosis that was 4 days old, this wide distribution of polymorphonuclear cells was particularly evident, though this number, great as it was near the lumen, was small in the region of the tunica muscularis. These cells also collected around the silk threads and were instrumental in having these slough into the lumen of the bowel. By the end of a week a large number of silk stitches were found virtually free in the lumen; at the end of three weeks only a few were observed, while at thirty days no sutures were seen. The infectious process undoubtedly accounted for their early separation and removal. However, the pus cells were also found in anastomoses which had completed their epithelial lining and were thus free, ostensibly, from continuous reinfection from the lumen. In specimens of 16, 86 and 133 days' duration, signs of acute inflammation were still present, but they were almost entirely limited to the subserous layer; the one exception was the inflammatory process around the silk threads situated in the submucosa and circular muscle coat; there the foreign body reaction predominated, and the polymorphonuclear cells were comparatively few. The muscle layers were least affected by the inflammation, and apparently had a peculiar ability to cope with the infection.

Blood Vessels.—The arrangement and number of the blood vessels at the anastomoses varied with the formation of the scar tissue. In the young anastomoses with their vascular granulation tissue, the blood-vessel pattern was irregular, and showed diffuse, numerous, small extravasations which were most marked in the submucosa. In the specimens that were 16 days old and older, the blood vessels in the newly formed scar tissue were somewhat large and not of the capillary size that predominated in the earlier specimens. With the contracture of the scar tissue and the approximation of the muscular layers, the blood supply also changed, and the net result of the change was that, when a large amount of scar tissue was present in an old anastomosis, this scar tissue contained vessels that were larger than those supplying the neighboring, normal muscle; when the end-to-end approximation of the various intestinal wall layers was good (and this held particularly for the tunica muscularis), then the blood supply of the region differed very little from the normal either in the number or the size of vessels (Fig. 13). All cases showed an increased vascularity in the tunica serosa.

Lymph Vessels.—Examination of the lymph channels that were filled with Berlin blue showed at the time of injection a typical, normal

pattern of vessels in the subserosa, which communicated with channels in the muscular coat. At the line of anastomosis the lymph vessels became larger, and communicated with a large trunk that paralleled the line of bowel union, continued into the mesentery and soon emptied into a lymph gland larger than the ones ordinarily found in such locations. The communication across the line of anastomosis was effected by a few, small vessels which were mainly in a subserous coat and, to a less extent, in the tunica muscularis and submucosa, as a subsequent examination of the sections and cleared specimens indicated. Solitary lymph follicles were also more numerous along the plane of bowel union than elsewhere.

Nerves.—From the anastomosis that had existed 177 days, a small block was cut at the time of necropsy and placed in 95 per cent. alcohol for subsequent staining of the Nissl substance; the remaining tissue was

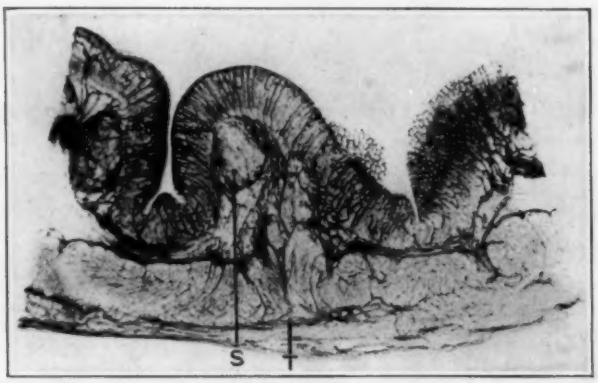

Fig. 13 (Dog A 8).—A cleared specimen of an anastomosis 177 days old showing the relation of the blood vessels, which are black in the healed tissues: the slight increase in the number and size of vessels at the anastomosis is noted; the muscle layers are fairly well approximated, and the vascular pattern around a solitary lymph follicle, *S*, frequently seen at the anastomoses, is also shown; × 7.5.

placed in liquor formaldehydi as previously mentioned. Examination of the ganglion cells in the plexus of Meissner failed to show any difference in the size or distribution of the Nissl substance from that found in the normal bowel. Furthermore, a search along the arteries and veins that extended into the line of anastomoses was also fruitless, in so far as it established absolutely the presence of young nonmedullated nerve fibers.

COMMENT

The basis for the majority of the recent methods for the aseptic end-to-end anastomoses of the large bowel has been the release of the ligating thread after the abuttal ends had been sewn together. This

was illustrated in the methods of Walker,[4] Halsted,[5] Foley,[6] Collins,[7] Fraser and Dott,[8] Horine,[2] Burket and McClure,[9] Highsmith,[10] Bidgood [11] and Grey.[12]. As stated before, the method used in all but one of these operations obviously presented nothing new as far as the fundamental idea was concerned; however, it is believed that the instrument used was not only original, but that it was also among the simplest of its kind. The idea of threading an instrument on the ligating thread was first advanced by Bidgood [11] and since that time reports of numerous instruments which could also be threaded on the ligature were published and suggested. Among these suggestions may be mentioned the one of Hughson [13] who passed the ligating thread through a loop of the cautery, and the one of Holman [13] who cut the ligating thread by means of a modified Gigli saw which had been included in the ligature.

The one operation in this series that was not performed with the special instrument already described was the one giving an anastomosis of four days' duration; it was done according to the method of Horine.[2] This method is very simple and would seem to merit more consideration. By suitably marking one of the releasing threads, as with a knot at each end, a possible confusion at the time of releasing the ligature can be obviated. With a view toward making the operation still simpler, for simplicity is the essence of all surgical technic, two successful operations were recently done, in which the ligating thread was simply cut by the scalpel. For it is plain that any elaborate and complicated apparatus like the one devised by Hartert [14] and sponsored by

4. Walker, F. B.: Intestinal Anastomoses; Presentation of a New, Simple and Aseptic Method, J. A. M. A. **51**:546 (Aug. 15) 1908.

5. Halsted, W. S.: Blind End Circular Suture of the Intestine, Closed Ends Abutted and the Double Diaphragm Punctured with a Knife Introduced per Rectum, Ann. Surg. **75**:356 (March) 1922.

6. Foley, F. E. B.: An Instrument and Method for Aseptic Anastomosis of the Intestine, Surg., Gynec. & Obst. **36**:836 (June) 1923.

7. Collins, F. K.: Aseptic Resection of Intestine, Ann. Surg. **76**:739 (Dec.) 1922.

8. Fraser, J., and Dott, N. M.: Aseptic Intestinal Anastomosis: With Special Reference to Colectomy, Brit. J. Surg. **11**:439 (Jan.) 1924.

9. Burket, W. C., and McClure, W. B.: Aseptic Method for Intestinal Anastomosis, Surg., Gynec. & Obst. **35**:816 (Dec.) 1922.

10. Highsmith, E. D.: Aseptic Resection of Intestine, Surg., Gynec. & Obst. **36**:27, 1923.

11. Bidgood, C. Y.: Blind End-to-End Anastomosis of the Sigmoid. A Modified Halsted Operation. Presentation of a New Instrument, Bull. Johns Hopkins Hosp. **34**:197 (June) 1923.

12. Grey, E. G.: Studies on the Aseptic End-to-End Anastomosis of the Intestine, Bull. Johns Hopkins Hosp. **29**:267 (Dec.) 1918.

13. Personal communication to the author.

14. Hartert, W.: Ein neuer Weg zur Wahrung volkommenr Asepsis bei Magendarmoperationen, Beitr. z. klin. Chir. **99**:475, 1916.

Schmiden [15] will not become part and parcel of the average surgical armamentarium.

Although numerous methods for the aseptic end-to-end anastomosis of the large bowel have been advanced, only a few reports of the anatomic findings have been given. The early studies of Halsted [16] and Mall,[17] and later the comprehensive report of Sabin on the anastomoses of the small bowel performed by Dr. Halsted and by Dr. Holman, were invaluable in calling attention to some of the fundamental considerations in surgery of the intestine. The importance of the submucosa, for instance, was evident to Halsted [16] as early as 1887, and the importance of this layer has again been emphasized by Graham.[18]

Fraser and Dott [8] have shown in a recent article some very good results obtained with their special instrument. Unfortunately, their report did not enter into a more detailed anatomic description, which their specimens obviously merited. Gara and Mandl [19] also reported a histologic study of the healing intestinal operation with special reference to the peritoneum.

Many of the observations made by these investigators regarding the regenerative processes of the small bowel are also true in regard to the colon. The epithelium showed the most marked proliferation, beginning early as in gastro-enterostomies (Flint [20]) and preventing further reinfection from the lumen. One can picture the cuticular border as developing from short cilia which get longer and have small knot-like enlargements at their extremity; finally, these terminal thickenings become so closely arranged that the appearance of a limiting membrane is obtained. That a difference of opinion exists regarding the cilia of the colon may be assumed from the fact that Schaffer [21] did not see any cuticular border, while Zimmermann [22] described not only a cuticular border but also long tapering ciliary projections.

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15. Schmiden, V.: Die Operationen am Darme, in Bier, A.; Braun, H., and Kümmel, H.: Chirurgische Operationslehre, Leipzig, Barth, 1920.

16. Halsted, W. S.: Circular Suture of the Intestine—An Experimental Study, Am. J. M. Sc. **94**:436, 1887.

17. Mall, F. P.: A Study of the Intestinal Contraction. Healing of Intestinal Sutures. Reversal of the Intestine, Johns Hopkins Hosp. Reports **1**:37, 1896.

18. Graham, A. J.: The Isolation of the Submucosa as an Aid in Intestinal Anastomosis, Surg. Gynec. & Obst. **38**:259 (Feb.) 1924.

19. Gara, M., and Mandl, F.: Untersuchungen über die Histologie der Darmmaht und der "Serosaplastik." Arch f. klin. Chir. **124**:419, 1923.

20. Flint, J. M.: The Healing of Gastro-Intestinal Anastomoses, Ann. Surg. **65**:202 (Feb.) 1917.

21. Schaffer, J.: Beiträge zur Histologie menschlicher Organ: I. Duodenum; II. Dünndarm; III. Mastdarm, Sitzber. d. k. Akad. d. Wissensch., Vienna, Math. Nat., Classe **100**:440 (Section 3) 1891.

22. Zimmermann, K. W.: Beiträge zur Kenntniss einiger Drüsen und Epithelien, Arch. f. mikr. Anat. **52**:552, 1898.

A peculiar feature of the cilia in cysts is worth special mention. In the epithelial cysts of which all the lining cells were flat (Fig. 9), the cilia of some of the epithelial cells were still long. It would have been reasonable to expect that the cilia would be at least shorter if not altogether absent under such circumstances. Their presence would indicate a peculiar resistance to the intracystic pressure and contribute support to the view that they are specialized structures of cell excretion.

It is believed that the young epithelial layer can arise from any part of the normal crypt, and that the base of the fundus is not the only part specialized for regenerating (Bizzozero [23]). Nor is it only the fundic one-third of the crypt, as Schaper and Cohen [24] observed, in which regeneration can take place; for, in a specimen in which the anastomosis was seven days old, the mouth of the crypt gave rise to a column of cells which extended over a part of the ulcerated area. In this particular group of cells, no goblet cells were seen to form, and it is reasonable to suppose that goblet cells will appear earlier if the epithelium is derived from the middle or from the fundus of the crypt; and later, if it is derived from cells at the mouth of the crypt.

Judging from the work of Amenomiya,[25] the healing of the ulcerated area in an anastomosis differs from the healing of the tuberculous ulcer of the bowel because, in the latter instance, the sheet of epithelium that first covers partially or completely the defect is subsequently covered over by a coat of cylindrical epithelial cells in one or more layers. In this communication and in all reports of the healing of experimental bowel lesions, only a single layer of epithelial cells is described as bridging the defect, and from this row of cells the glands characteristic of that portion of the bowel developed.

The comparatively late differentiation of mucus by the young epithelial cells would indicate that the primary object of the regeneration was to cover the defect and establish communication, whereas it was of secondary importance to have mucus formed for the protection of the cells. Since mucous cells were practically absent in the epithelial lining of the cysts, it is believed that these cells are sensitive to increased pressure and that their differentiation can be suppressed by such

23. Bizzozero, G.: Ueber die schlauchformingen Drüsen des Magendarmkanals und die Beziehungen ihres Epithels zu dem Oberflächenepithel der Schleimhaut, Arch. f. mikr. Anat. **40**:325, 1892.

24. Schaper, A., and Cohen, C.: Ueber zellproliferatorische Wachstumzentren und deren Beziehungen zur Regeneration und Geschwulstbildung. Arch. f. Entwcklngsmechn. d. Organ. **19**:348, 1905.

25. Amenomiya, R.: Ueber die Regeneration des Darmepithels und der Lieberkühnschen Krypten an tuberkulösen Darmgeschwüren, Virchows Arch. f. path. Anat. **201**:231, 1910.

measures. In this connection, it may be recalled that Ribbert [26] reported the disappearance of goblet cells of the conjunctiva in corneal transplants.

The muscularis mucosae did not show the same powers of regeneration reported by Mall [17] and Sabin [27] for the small bowel. The reason for this discrepancy probably lies in the fact that in the colon the inflammatory reaction was more severe and continued longer than was the case in the small intestine. For that reason, the sharp breaking through of the glands on the submucosa which Sabin observed was not seen.

The ability of the tunica muscularis to form new muscle has been repeatedly denied. From a review of the subject made by Goldzieher and Makai [28] in 1912, the impression is gained that plain muscle does regenerate, though only to a slight degree. More recently, Barry [29] has showed again that regeneration in plain muscle takes place; the material for this report also supports this view.

The marked thickening of the circular muscle layer proximal to the anastomosis (Fig. 12, *C*) is difficult to explain. Obviously, a partial obstruction at this point would cause hypertrophy of the muscle layers because of the extra work placed on them. But, as the figure clearly shows, the construction was slight, and since the anastomosis was 86 days old, there would seem to have been ample time for an adjustment approaching the normal. It is not reasonable to suppose that the second anastomosis gave rise to a hypertrophy which extended to either side of it. The explanation offered by Rindfleisch [30] to the effect that the hypertrophy is due to a disorderly muscular arrangement does not apply.

As a rule, there were adhesions at the line of union. However, in three cases no adhesions were found (Fig. 1), and the explanation for this may be found either in the improved technic employed in those particular cases, producing a negligible damage to the mesothelium, or in the resolution of small and slight adhesions whose attachment was only temporary. The remarkable extent to which the peritoneal mesothelium may react toward a chronic irritation has recently been

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26. Ribbert, H.: Experimentelle Erzeugung von Epithel und Dermoid-cysten, Deutsch. Ztschr. f. Chir. **47**:575, 1898.

27. Sabin, F. R.: Healing of End-to-End Intestinal Anastomoses with Especial Reference to the Regeneration of Blood Vessels, Bull. Johns Hopkins Hosp. **31**:289 (Sept.) 1920.

28. Goldzieher, M., and Makai, E.: Regeneration, Transplantation und Parabiose, Ergeb. d. allg. Path. u. path. Anat. **16**:344, 1914.

29. Berry, F. B.: The Regeneration of Smooth Muscle Cells, J. M. Res. **41**: 365 (March) 1920.

30. Rindfleisch, W.: Experimentelle Untersuchungen über die Heilung des Darmes nach Resektionen bei Anwendung Czerny-Lembertscher Nähte, Arch. f. klin. Chir. **46**:600, 1893.

shown by Cunningham;[31] it is thus highly probable that the freedom from adhesions is in a great measure due to the remarkable powers of proliferation possessed by the serosal cells of the peritoneum.

Of particular interest was the inflammatory reaction at the anastomosis. The inturned bowel edge was at once exposed to a host of infecting organisms, which rapidly invaded the tissue at the line of union, then possibly worked their way between the approximated muscle layers and peritoneum, to bring evidence of an acute infection at the serous membrane.

It cannot be stated whether the contamination about the sutures was due to the fact that the particular stitch had entered the lumen or whether the infecting organisms had worked their way to the thread from the ulcerated area; nor can it be decided from the few cases reported here, whether this extensive, acute, inflammatory reaction was an accidental occurrence or whether it was characteristic of the early stages of healing in the bowel. However, the gradual subsidence of the signs of inflammation took place with the increasing age of the anastomosis; the scar tissue contracted and approximated more closely and firmly the respective bowel layers, while the polymorphonuclear cells became progressively less. The fact that the bowel wall is well adapted to combat infectious processes arising from the lumen was illustrated by the presence of hairs in dense scar tissue situated opposite the tunica muscularis in the specimen 98 days old. In all probability, these hairs were first in the lumen and were later enmeshed in the scar tissue; that they were accidentally placed there during the operation seems unlikely. They certainly were infected foreign bodies at first, but they subsequently lost their signs of infection.

Another foreign body, the silk thread, was a favorite material for infection and was surrounded by polymorphonuclear cells for at least sixteen days after the operation. By the end of this time, however, a large number of foreign body giant cells were also present, aiding in the removal of the material. The black color disappeared first from the thread when the material was embedded in muscle. In some specimens older than 30 days, the silk was free from any acute inflammatory reaction; however, it was encapsulated. That the thread was infected at first and later had its infecting agents destroyed is only a conjecture, but it is believed that this process did take place to some extent.

The greatest stress has always been placed, possibly needlessly so, on the strict aseptic release of the ligating thread. Undoubtedly, the more aseptically any operation is performed the better will be the healing;

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31. Cunningham, R. S.: The Effects of Chronic Irritation on the Morphology of the Peritoneal Mesothelium, Bull. Johns Hopkins Hosp. **35**:3, 1924.

in this case, it must be remembered that the numerous stitches, unfortunately, were not always taken in the submucosa alone as it was intended, but that they also entered the lumen of the bowel. Accordingly, contamination occurred, and the effect of the strictest technic used in dealing with the blind ends of the bowel was vitiated by the sutures. Of course, it may be said that faulty technic was responsible for the inflammatory reactions, and nothing can be offered to disprove this statement except the presentation of several specimens (Figs. 1, 2, 3, 4, 10, 11) which show good operative results. It may also be claimed that it is better to include the mucosa in the stitch in case of doubt and obtain approximation with infection, rather than to include only the tunica muscularis and have separation of the stumps with the inevitable fatal peritonitis.

It is also believed that the time for the disappearance of the infection depended on the position of the thread; for, if it were buried in the substance of the bowel it would become free of infection early; whereas, if one end were fixed in the bowel wall and the other projected into the lumen then the stitch would be infected for a very long time. In all the specimens, many of the silk threads were cast off into the lumen of the bowel by the seventh day; by the twenty-first, according to a case not reported in this series, the majority had disappeared. Only a few stragglers remained because they were attached to the submucosa; otherwise they were hanging free in the lumen. Undoubtedly some, certainly very few, were cast off towards the peritoneal surface; in the specimen of 213 days, part of a stitch was seen in a section of the tunica serosa.

Not only silk but also catgut can remain for a long time in the anastomosis according to Fraser and Dott,[8] who observed traces of 0000 tanned catgut from seventy to eighty days after the operation.

As regards the question of using one, two or three rows of stitches, it is safe to say that one row, properly placed to include some of the submucosa, is sufficient in the experimental animal. In the human subject, however, the colon is much larger, and therefore a second row will amply reinforce the first row without causing too much obstruction. Obviously, every additional row will cause a greater inturn and obstruction, besides giving a greater area for fibrosis and constriction. The small number of stitches necessary for anastomosis was shown by Merrem,[32] in 1810, who excised the pylorus in three dogs, anastomosed the intestine with three stitches, and secured perfect healing.

Proper ligation of the bowel was an important step, because the thread not only occluded the lumen but also severed the tunica mus-

32. Merrem: Animadversiones quaedam chirurgicae experimentes in animalibus factis illustrata Giessae, 1810, quoted by Halsted (Footnote 5).

cularis and promoted an end-to-end apposition of the various bowel layers. In the one case in which one anastomosis was made after sectioning the tunica muscularis according to Schoemaker [33] and another anastomosis was made by the ordinary method, the results were practically the same (Fig. 1).

The procedure of previously crushing the bowel should also be questioned unless the destroyed tissue be situated between the ligature and the stump. Obviously, every additional amount of dead tissue increases the infectious process and the sloughing.

SUMMARY

Material obtained from twelve aseptic end-to-end anastomoses of the large bowel of nine dogs is reviewed. It was found that the epithelial lining was restored by the sixteenth day in favorable cases, and that in a specimen 30 days old normal crypts of Lieberkühn had formed to such a degree that they rendered the identification of the line of bowel union impossible from inspection of the mucosa alone. The young epithelial cells were at first flat, but later took on a cuboidal and finally a cylindrical shape. Goblet cells differentiated relatively late depending on the position in the crypt of the cells giving origin to the new epithelium.

From observations on the ciliated structure of the newly formed epithelial cells, the hypothesis was advanced that the cuticular border began as short cilia. Formation of small cysts at the anastomosis was the rule. The muscularis mucosae showed definitely impaired restitution, while in the young anastomoses the submucosa was the seat of ulceration which later gave way in the older specimens to a fibrous tissue reaction with a corresponding vascular supply. The good approximation observed in the tunica muscularis or the anastomoses of long standing was due mainly to a contraction of the intervening scar tissue and, in a less degree, to proliferation of the muscle itself. That the operations were not aseptic was shown by the presence of an acute inflammatory reaction extending the entire thickness of the wall, in cases of from 4 to 16 days' duration, due to contamination from the raw surface exposed to the lumen and from infected sutures. Specimens 30 days old or older failed to show this extensive reaction. The constriction at the line of union was greater when the bowel was small, but in all cases it decreased with age. The majority of the silk sutures were found to be passed into the lumen. Finally, a brief discussion of some of the factors entering into the healing process is given.

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33. Schoemaker, J.: Some Technical Points in Abdominal Surgery, Surg., Gynec. & Obst. **33**:591, 1921.

INJURY, INCLUDING IRRITATION, AND CANCER*

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About two years ago [1] I presented, as concisely as I could, evidence that, of all the suggested causes of cancer, irritation had best stood the tests of clinical observation, statistical study and experimental research. Facts published since that time have brought forward no conclusive controverting evidence, and much that has appeared supports the contention then advanced. Among the data then presented I briefly referred to: chimneysweeps' cancer; smokers' cancer; betel-nut chewers' cancer; soot cancer; pitch-workers' cancer; tar cancer; charcoal-burners' cancer; anthracene cancer; anilin dye cancer; grease-workers' cancer; arsenic cancer; buccal cancers due to dental irritation, faulty dentures, etc.; roentgen-ray cancer; sheep-dip cancer; cancers arising on occupation dermatoses, and on tuberculous, blastomycetic, leptothritic, syphilitic and other chronic irritative processes; experimental cancer, including malignancy induced by tar and tar products and by parasites; cancer associated with bilharziasis; scar sarcomas; keloid; irritation neuromas; cancers following burns; solar influences in the production of skin cancers; cancers following acute injury; cancer superposed on chronically irritated essentially benign processes, as angioma and papilloma; manure warts and cancers; cancer developing on chronic or at least prolonged ulcerative processes of certain types, such as chrome holes, chrome ulcers, chrome eczema, pellagrous ulcerations and oriental sore; cancer arising on gastric ulcer; gallstones and cancer; cancer arising in intestinal diverticula; cancer occurring in chronically inflamed appendixes; slaters' cancer; lathers' cancer; injury and irritation of the nipple and mamma, and chronic inflammation of these structures followed by cancer; injury, irritation and inflammation in relation to cancer of the female genitalia; preputial and other penile cancers; irritation in laryngeal cancer; cancer of the lung associated with gross foreign bodies, irritating dusts and chronic infection; and observations showing an intimate relation between irritation and cancer.

Noteworthy supporting facts have since appeared. In the field of experimental cancer production, previous work has been repeatedly corroborated, and cancer has been successfully induced in animals under

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1. Coplin, W. M. L.: A Basis for the Prevention of Cancer, J. A. M. A. **78**:1523 (May 20) 1922.

conditions that leave no obvious doubt. Begg [2] reports a study of 140 tar tumors in animals and shows that such tumors follow closely the well known features of malignancy seen in man; metastases occur as in human carcinoma, involving lymph nodes, manifest permeation extension and even spread by the perineurium (18.5 per cent.), a form of invasion not uncommon in certain types of cancer in man. Leitch,[3] of London, has demonstrated that the oils believed to be the irritating causative agents in "mule-spinners'" cancer of the scrotum are able to produce cancer in mice. Of 188 animals experimented on, Yamagiwa and Murayama [4] have produced cancers in twenty-three, about 12 per cent. Bittmann [5] has also produced tar cancer in rabbits.

So far, we are no nearer accurate knowledge of the carcinogenic body responsible for tar cancer. In my earlier paper I called attention to this hiatus in our evidence and to the assumption by some that, as in the case of anilin cancers in man, the causal substance has been thought to be arsenic, a view to which Bayet [6] also subscribes, although this contention is not acceptable to many observers. It has been demonstrated [7] that a number of pure, or fairly pure, coal tar derivatives are not carcinogenic. Ullmann [8] produced warts in the vaginal mucosa of a female dog by inoculation with extract derived from a laryngeal papilloma in a child. To this experiment I shall again refer.

Although experimental carcinoma has been established by many observers,[9] the production of sarcoma has been less often successful. In my former paper I referred to the success of Bullock and Curtis and should have mentioned the fact that the first sarcoma experimentally observed was reported by Ehrlich and Apolant,[10] who believed that it arose from malignant transformation of the stroma of a transplanted tumor orginally apparently a pure carcinoma. Marie, Cunet and Raulot-Lapointe (cited by Russell) saw sarcoma develop in the tail of a rat after repeated roentgen-ray exposure. Russell [11] has produced

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2. Begg: Imperial Cancer Research Fund; Eighth Scientific Report, London, 1923; also detailed bibliography.

3. Leitch, Archibald: Brit. M. J. **2**:1104 (Dec. 9) 1922.

4. Yamagiwa and Murayama: J. Cancer Res. **8**:119 (April) 1924.

5. Bittmann: Casop. lek cesk. **63**:177 (Feb. 2) 1924; abstr., J. A. M. A. **82**:1010 (March 22) 1924.

6. Bayet: Le Cancer, J. belge d'etudes cancerlogiques **1**, Nov. 15, 1923.

7. Kennway: Brit. M. J. **1**:564 (March 29) 1924.

8. Ullmann: Acta Oto-Laryngologica **5**:317, 1923.

9. The bibliography is given in the former paper (Footnote 1); also, in Begg (Footnote 2), Leitch (Footnote 3) and in other references cited in this paper.

10. Ehrlich and Apolant: Berl. klin. Wchnschr. **43**:37, 1906.

11. Russell: Imperial Cancer Research Fund; Eighth Scientific Report, London, 1923, p. 65.

sarcoma in rats and mice by repeated subcutaneous inoculations of coal tar. The long period during which evidence of actual or potential malignancy is lacking (latent period) is most interesting; one rat had received weekly inoculations for a year, but the neoplasm, an osteosarcoma, did not attract attention until six months later. Such prolonged latent periods no doubt often render impossible a correct clinical association of the injury with the new growth in man. It is quite certain that few clinicians, if any, would admit the existence of a relationship between trauma or irritation of any type and a malignant growth that did not manifest itself for months or even years after injury, after apparent arrest of irritation or after the unknown action of some previously long continued irritant. Furthermore, to obtain such data in history-taking is usually difficult and often impossible.

As to clinical studies, considerable information has been added recently; much is of great value, and some was previously unknown. In their study of cancer of the scrotum, Southam and Wilson [12] find in the records of the Manchester Royal Infirmary for the last 20 years 141 cases; of these one was in a chimney-sweep, twenty-two cases among tar and paraffin workers, and sixty-nine of the patients were "mule-spinners." The last named embrace a group whose occupation requires the workman to come in contact with machinery in such a manner that the left groin and scrotum are soiled with lubricating oil which, with the associated friction, leads to cancer; there is frequently a long, latent stage, and often a dermatosis followed by a final malignancy. Leitch [3] has shown that such oils produce malignant disease in mice.

Of thirty-two cases [13] of chrome ulceration three resulted in death from epithelioma. It is also suggested that dermatitis of other etiology, such as that produced by celluloid substitute, shellac varnish, the cracking of Brazil nuts, orange peeling, lubricating oils, phosphorus sesquisulphid, or similar influences, should be watched as carefully as the dermatitis produced by chrome preparations.

Scott [14] has made a most exhaustive study of paraffin-workers' cancer, including the precancerous or occupation dermatoses; the investigation embraces observations extending over twenty-four years in an industry employing approximately 200 men, where the constancy of certain factors has been known for half a century. Among workers, there is a striking difference in susceptibility not only to the occurrence of the peculiar dermatoses but also to the incidence of malignancy in those in whom skin lesions have already arisen; there appears to be

12. Southam, A. H., and Wilson, S. R.: Brit. M. J. **2**:971 (Nov. 18) 1922.

13. Factory Hygiene: Annual Report of Chief Inspector, Brit. M. J. **2**:466 (Sept. 15) 1923.

14. Scott: Imperial Cancer Research Fund; Eighth Scientific Report, London, 1923, p. 85.

some inborn factor. Many dermatoses are illustrated, numerous illustrations showing various stages in the evolution of lesions. Long latent periods are well known; it is often difficult, or impossible, to determine the exact time when a dermatosis became malignant. The same agents have been used to produce cancer in mice; in these animals, the earliest appearance of a wart was on the eighty-third day; "when the length of life of a mouse is compared with that of man, the development of malignant conditions takes the same time proportionately in the mouse as in man." [15] In man long periods of latency occur, warts appear and disappear and, in some cases, the lesions persist long intervals after the cessation of paraffin work; one case is illustrated in which many warts were present fifteen years after the patient had given up employment. The paper is most interesting in that it gives in detail the protective measures that have been taken in the Scottish Shale Oil Industry.

That cancer produced by chronic irritation may be characterized by great chronicity is well known, but that it may become speedily and intensely invasive is not so generally recognized. In a creosote cancer of the dorsum of the hand recorded by Cookson,[16] the growth had been of "certainly fifteen" years' duration, but when a postmortem examination was made "seven or eight weeks" after the amputation of the arm above the elbow, a widely spread metastasis was found; most unusual in a case of squamous epithelioma, there were nodules in the heart, one the "size of a walnut" involving the entire thickness of the left ventricular wall and projecting into the cavity; the lungs, liver, both kidneys and, of course, many lymph nodes were also involved.

Naturally, irritation often determines a striking constant distribution of cancer; although this is well shown in cases of smokers' cancer and in the occurrence of growths produced by soot, paraffin and oil, such as those found in mule-spinners, etc., it is sufficiently striking to be especially noteworthy in the case of kangri burn cancer. Neve [17] found that in the Kashmir Mission Hospital, of 2,491 operations for epithelioma, approximately 2,000 (84 per cent.) were for kangri burn cancer. Kangri stoves are earthenware bowls from 5 to 6 inches (12 to 15 cm.) in diameter, charcoal heated, enclosed in wicker, and carried under the single loose garment of the poorer classes. Neve thinks the primary factor is heat, but the products of combustion cannot be excluded. Since these stoves are suspended below the abdomen and in front of the thighs, the irritant action is manifested in the skin covering these areas, and here practically all the cancers originate.

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15. Scott: Imperial Cancer Research Fund; Eighth Scientific Report, 1923, p. 116.

16. Cookson, H. A.: Brit. M. J. **1**:368 (March 1) 1924.

17. Neve, E. F.: Brit. M. J. **2**:1255 (Dec. 29) 1923.

The age incidence is about 55, and the growths are considerably more common in men than in women because the latter do not carry the stove so much in the house. It usually begins as a well-defined precancerous metaplasia, keratinization, a warty thickening with, later, fungating or ulcerative processes, and it may be multiple. Gland involvement rarely appears early, and sometimes is long delayed.

DuBois [18] found that 97 per cent. of 200 skin cancers were on the face; the almost constant presence of demodex in patients over 20 suggested a possible relation with cancer. The prevention of cancer embraces a most careful supervision of follicular keratoses, vegetations and proliferations. DuBois believes that cancers of the tongue and rectum are, in almost every case, associated with syphilis.

Spittel [19] has added definite observations on the relation of betel-nut chewing to buccal cancer; those who begin the nut chewing when they are young have cancer early; he has often seen it in patients between 25 and 30 years of age. Cancer of the mouth, so rare among European women, is by no means uncommon in Colombo. The latent period may be either short or greatly prolonged, and leukoplakia may exist for years without cancer. It would be interesting if clinical and experimental investigation indicated that leukoplakia is really a protective reaction, presenting itself when actual cancer does not develop.

Peill,[20] working in China, has seen cancer of the tongue but not of the lips. He attributes the absence of labial carcinoma in China to the exclusive use of long stem pipes, and to the fact that the stems are smooth and nonabsorbent. This observer thinks that in China the frequency of cancer of the esophagus may be due to drinking "frightfully strong, undiluted spirits hot"; this also might be a factor in the production of gastric cancer, which Peill says is fairly common.

Although much has been added to our knowledge of cancer of the bladder and rectum produced by bilharzia irritation, a dominant influence stressed by Dolbey and Tähney [21] is not so well known; the papillary hyperplasia or true papilloma of the rectum may persist or even increase after the destruction of parasite and ova by tartar emetic; the growth may recur after any removal short of complete excision. This is another evidence of a fact to which I have repeatedly called attention, namely, that persistent irritation establishes some cytologic change in the reacting elements, which persists after the withdrawal of the initial irritant, and that it may be manifested by the development

18. DuBois, C.: Revue méd. de la Suisse Rom. **43**:802 (Dec.) 1923.

19. Spittel, R. L.: Brit. M. J. **1**:158 (Jan. 26) 1924.

20. Quoted in a letter by Sidney Davies: Brit. M. J. **1**:131 (Jan. 19) 1924.

21. Dolbey and Tähney: Lancet **1**:487 (March 8) 1924. Dolbey and Moore: Lancet **1**:587 (March 22) 1924.

of malignancy at some remote period. This phenomenon is seen in cases of anilin cancer, soot, paraffin and tar cancer (both natural and experimental), apparently in smokers' cancer and, no doubt, in some if not in many other irritation malignancies. It greatly increases the practical difficulty in determining the relation of cancer to some more or less remote acute injury or chronic irritation.

From the literature I have found many cases recorded in which irritation was followed by cancer so closely and intimately associated that the cause and the result of the relationship appear unmistakable. Some are very suggestive of this relationship, but are not adequately

Fig. 1.—Irritation wart on the middle finger of the right hand. The finger was crushed and mutilated in childhood. Unfortunately, the matrix of the nail was not destroyed and, after recovery, nail growth appeared on the end of the stump; this occurred at about the fifth year. In the course of several years (exact period not known), the thickened, rather sharp point of the nail (*B*) grew downward toward the palmar aspect, impinged on the skin and caused irritation; within the next few years, a wart (*A*) gradually developed and often became inflamed. The patient learned to keep the nail cut back as it is shown in the figure; after that the wart lessened in size and became rather soft, but after more than forty-five years it still remains. The patient is now 60 years of age and suffers no inconvenience from the deformity or the wart, provided the nail is kept properly trimmed. Clearly, the wart should be removed, and removal of the deformed nail is also recommended. Numerous other scars on the hand and cicatrices elsewhere on the face, body, legs and feet present no signs of abnormality; however, no other location has been subjected to continued or repeated irritation.

recorded, as, for example, a case of cancer of the skin which was produced about a tube held for a long time in place during the drainage of a gallbladder or an empyema; the case records, in this instance, do not exclude implantation from deeper growth. In still other instances, this relationship is, to my mind, more clearly shown. Murphy [22] reports a case and collects twelve others in which cancer has arisen in exstrophy of the bladder; the vesical mucosa must be constantly irritated in cases of this malformation. Patrick and Burton [23] record four cases of sarcoma, in which trauma or irritation was the cause; these four factors were the roentgen rays, carbon dioxid snow, scraping with Volkmann's spoon, and a blow received from a mass of coal. They believe the evidence conclusive that the growths were not necessarily malignant from the onset. In the literature, recognition of this fact is repeatedly and timidly asserted, largely because the ecology [24] of tumors, particularly in regard to the relationships here discussed, is not generally apprehended or widely studied. Parrish reports an epithelioma of the auditory canal as an end-result of chronic otitis media of forty-two years' duration.

The tendency of many occupational dermatoses and precancerous manifestations to begin as papilloma or "warty" growth is quite the rule. Although most are not true papillomas, some may be. Surely, irritation is a recognized factor in the production of warts. Figures 1 and 2 are illustrations of this fact. Venereal warts and warts containing demonstrable organisms are probably irritation responses, often hyperkeratinizations rather than true warts. The inoculability of some forms is well known; one of the most interesting reports on the subject is by Ullmann,[25] who, using an extract of laryngeal papilloma from a boy aged 6 years, inoculated his arm and the vagina of a dog; papillomas developed at both inoculation sites and, from his own arm, the observer successfully inoculated the arm of a friend; the latent period was "several weeks" with the first transfer and, on the friend, "barely five weeks." During the removal of the growth from the larynx, the boy's upper lip was injured, and at that point, three and one-half months later, a papilloma developed which spread to the face. The secondary growths varied with the nature of the tissue affected. Ullmann, according to other facts given, concludes that the virus is ultramicroscopic. Antecedent irritation is an admitted factor in the production of papilloma

22. Murphy, Douglas P.: Exstrophy with Cancer of Bladder and Absence of Umbilicus, J. A. M. A. **82**:784 (March 8) 1924.

23. Patrick, J., and Burton, J. A. G.: Glasgow M. J. **100**:8-18 (July) 1923.

24. A term used for what he calls the habits of tumors, by Sir John Bland-Sutton: Brit. M. J. **2**:847 (Nov. 10) 1923.

25. Ullmann: Acta Oto-Laryngologica **5**:317, 1923. Brit. M. J., Jan. 19, 1924, epitome p. 11, abstr. 59. Older references may be found in Gaskill's revision of Stelwagon's "Diseases of the Skin," Ed. 9, Philadelphia, 1923, p. 575.

of the larynx in children, although nothing definite is known concerning the etiology.[26]

Venereal warts, warts formed about foreign bodies such as fragments of glass that have become embedded in the skin, warts manifested in the evolution of tar dermatoses and allied conditions, bilharzia warts of the bladder and rectum, and warts such as those shown and described in Figures 1 and 2 do not have the specific origin of a gumma or a tubercle, but represent a nonspecific response to irritation. Whether they will become cancerous or not, in any given instance, probably can never be foretold; it seems probable that malignancy is determined by

Fig. 2 (Case 2).—Irritation warts probably produced by lubricating oil and associated mechanical irritation.

some inbred susceptibility or by some inherent character of the tissues, by the nature and duration of the irritant reaction, or by a succession or a combination of such factors, the exact nature of which remains unknown. Nevertheless, it is most important for medical men to recognize that these growths, in common with many other tissue responses to irritation, may in any particular case be forerunners of malignancy; that the appearance of definite cancer may be long delayed or it may be rapid, and that delay in treatment is not only unwise but unjustified and dangerous.

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26. Crowe, S. J., and Breitstein, M. L.: Papilloma of the Larynx in Children, Arch. Surg. **4**:275 (March) 1922.

Since critics may infer that there is undue lack of information on my part, I may say that the admission that many of these so-called warts are keratoses rather than true papillomas does not invalidate the statements made, but adds confusion to their practical application to the prevention of cancer, and only obscures where obscuration is to be avoided.

So far as I know, no one maintains that smokers' cancer, soot, paraffin and all such cancers, including mule-spinners' cancer and allied types of malignancy naturally occurring in groups, are contagious in the sense that a communicable disease is transferable. In cases in which there are indications of communicability in cancer, such as in cancer houses, cancer epidemics, etc., the cause may be traced to the common action of some irritant; this has been suggested by Regaud.[27]

Smokers' cancer, like kangri stove cancer, has been attributed to the action of heat, but it is not improbable that both depend on the presence of some agent resulting from combustion. It is also possible that tobacco may contain, or that there may be evolved during its combustion, a carcinogenic substance. The following case illustrates a vagary in the location and spread of a smoker's cancer:

REPORT OF CASE

CASE 1.—X, a physician, aged 51, a patient of the late Dr. William J. Roe, had been a constant user of tobacco since youth. He smoked a great deal and when he was not so engaged, he carried a small quid of chewing tobacco between the lower lip and the gum, and another piece under the tongue behind the lower incisors; these quids he discharged before eating and immediately resumed as soon as he was obliged to discard his after-meal cigar or pipe. About nine weeks before coming under observation, the patient had noticed tenderness and irritation just back of the central incisors, from what he thought was a nodule; ulceration rapidly extended between and around the teeth involved, so that it was impossible to be certain whether the growth began on the lingual or on the labial aspect. At no time was the upper part of the lower lip or any part of the tongue involved. The loosened teeth were removed; extension into the soft parts of the chin occurred and, when the patient was operated on, the subcutaneous growth presenting externally appeared red and inflamed; necrosis and external ulceration seemed impending. It was not thought that any glandular invasion was present. The family history was negative; there was no evidence of, and the patient said he did not have, syphilis. The process was obviously malignant. Radium was tried at an early date, but the technic at that time was crude, and no apparent benefit resulted.

Under ether anesthesia Dr. Roe did an extensive removal, with wide excision of the soft parts; he sawed through the jaw lateral to the bicuspid, removed the submaxillary glands and, as far as possible, all contiguous lymph node bearing tissue (Fig. 3). For our purposes, the operation need not be described. The patient failed to make a good recovery, developed pneumonia and died seven days after the operation.

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27. Quoted by Tiessenger: Bull. de l'Acad. de méd. **91**:284 (March 4) 1924.

The extreme lower part of the specimen shown in Figure 3 is the mucosal border of the lower lip, notably retracted and not at all involved. Just above is the wrinkled buccal mucous membrane. There is a deep excavation (*A*) resulting from radium destruction and the removal of a portion for histologic study; on each side of this cavity an incisor and a bicuspid are still in place; external to each bicuspid is the socket of a tooth extracted at operation and beyond the outer ends of the

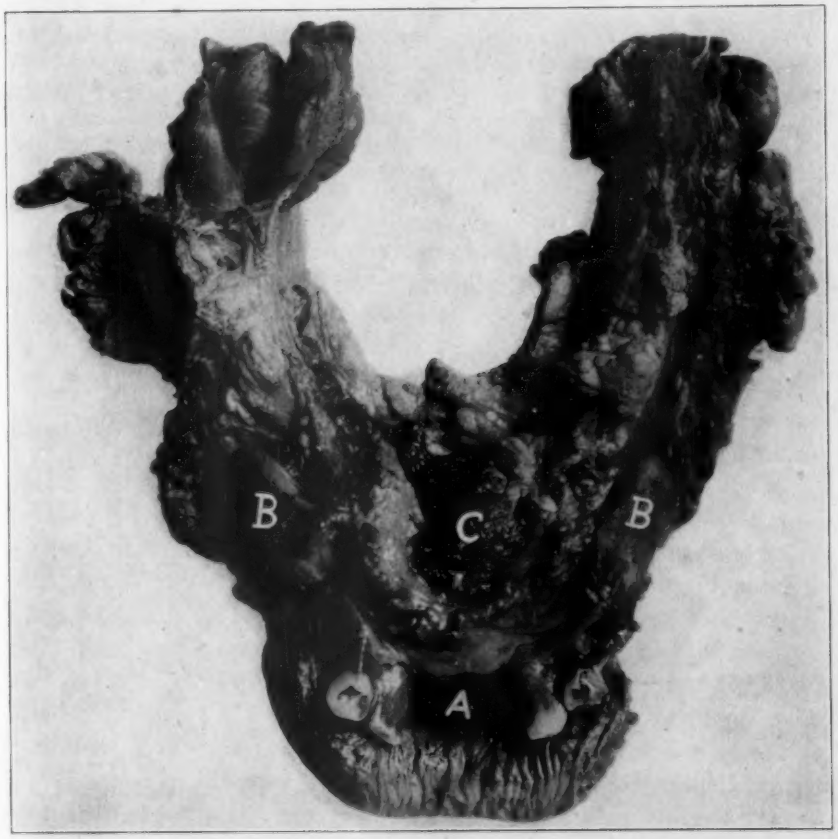

Fig. 3 (Case 1).—Excised part of lower jaw and attached soft parts, removed by Dr. Roe (photograph of specimen in Museum of the Jefferson Medical College), in a case of cancer in a user of tobacco: *A*, an excavation resulting from radium destruction and removal of a portion for histologic study; *B*, outer ends of sectioned jaw; *C*, the cancer mass.

sectioned jaw (*B*, *B*). The cancer mass (*C*) is back of the lingual aspect of jaw. On each side there are masses composed of the submaxillary gland and other soft parts that extended into the anterior triangles of the neck. The oval space lying between these upward-projecting masses was occupied by the tongue and other soft tissues of

the floor of the mouth, left behind and sutured in position to the unexcised parts of the jaw, and to contiguous structures involved in the wound.[28]

The histologic examination indicated (1) that the growth was a squamous cell epithelioma, (2) that there was involvement of the mandible about and below the teeth, (3) that no invasion could be demonstrated in the bone at the severed ends, (4) that there was extensive invasion of the soft parts through and into the skin covering the chin, (5) that there was no infiltration of the submaxillary salivary glands, (6) that the small lymph nodes contained metastases, (7) that there was a perineural infiltration in one small nerve, (8) a very marked lymphocytic and some polynuclear permeation of the neoplastic structures and the contiguous soft parts. If the patient had survived recurrences would have been inevitable, because the extensive lymph node metastases found would have made it probable that residual smaller masses would be left behind notwithstanding the fact that excision had been done.

This, then, was a case of cancer in a user of tobacco, the growth originating in structures that could not have been subjected to heat injury, and apparently justifying the belief that the irritant acted at the points of injury produced by the masses of chewing tobacco carried in the mouth, and that, of course, these points were frequently, if not constantly, permeated by such extracted derivatives of combustion as entered the saliva or by gravity reached the semisolid collections; this resulted in an irritation cancer, with the customary uncertainty as to the exact nature of the irritant.

It is interesting to observe that, although Dr. Roe recognized the probable cause, the hospital history, taken by a capable intern, contains no intimation of the relation. Such a record is not uncommon; those seeking the cause often, though not invariably, find it, while the casual historian fails to detect or to note a highly important connection. Such a striking body as a lithopedion [29] is recorded as having a causal relation to malignancy; a calcified mass of a smaller size or of a less striking nature escapes record. Cancer of both breasts associated with years of crutch injury [30] attracts attention; traumas resulting from the use of stays or other appliances are forgotten by the patient, and either overlooked or ignored by the historian.

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28. Since this article was prepared (spring of 1924) several studies have appeared entirely confirmatory of the previously adduced evidence of the close association of cancer and irritation. Most important among these should be mentioned the work of Archibald Leitch (Brit. M. J. **2**:451-454 [Sept. 13] 1924) on the experimental production of cancer of the gallbladder in guinea-pigs, animals in which cancer is not known to occur in nature. Leitch also gives numerous references.

29. Auvray: Gynéc. et Obst. **9**:346 (April) 1924.

30. McGraw, R. B., and Schraukel, Rupert: Bilateral Cancer of the Breast in the Female Following Prolonged Irritation, J. A . M. A. **82**:2028 (June 21) 1924.

CASE 2.—The patient, aged 29, an aviator, gives personal attention to his motor. While he is cleaning and adjusting the parts he wears a heavy, rather coarse cotton glove. The ulnar aspect of the glove becomes saturated with dirty oil, and the coarse fabric appears to act as an associated mechanical irritant. Warts have appeared over his knuckles, and at the margin of one nail there is a small wart (Fig. 2). The warts are, for the most part, hard, with, in some, dense keratinization of the most superficial layer. One or two are developing on the palmar aspect also. At this man's age, these lesions are probably without danger; they show practically no regression after six months in which the patient has done little or no flying; they are not disappearing on the withdrawal of the irritation and removal is recommended. Obviously, this patient runs considerable risk in exposing his hand to the continued action of this particular irritant.

We are not yet in possession of all the data, and it may be that there is something quite subtle and elusive, only vaguely if at all anticipated, awaiting discovery. The evidence [31] that cancer is a specific response to infection or to some parasite of a higher order is, to me, as yet quite inconclusive, but if by chance future investigation should surprise us by such a revelation, the application of existing knowledge of the dominant part played by trauma and irritation in the production of many malignancies would lose none of its practical value in the prevention of malignant disease. The fact remains that, for the reduction of cancer incidence and the early treatment, by operation or otherwise, and the consequent systematized attack on malignancy, the cure of conditions prone to evolve into malignancy and the early and effective treatment of cancer thus evolved can be best promoted by a general recognition and a wide promulgation of the fact that injury of certain types and irritation of fairly definite forms are today most important factors for clinicians to associate when considering the possibilities of any particular case. A knowledge of such relations must be disseminated and thoroughly impressed on the lay mind and on health officers; this will lead to the use of prophylactic measures and to the impressing of the laity with the necessity for wise counsel frequently obtained, to the avoidance of cults and quacks, and to prompt action at a time when such action is often of the utmost importance.

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31. Coplin (Footnote 1). Young (Med. Chir. Soc. Edinburgh, Brit. M. J. **1**:862 [May 17] 1924) later studies bacteria in cancer, and the apparent skepticism of Prof. Gulland and Sir Harold Stiles is shown. There is a pithy correspondence between Brand and Leitch (Brit. M. J. **1**, May 24, 1924; **1**:983 [May 31] 1924; **2**:1029 [June 7] 1924) in which the former holds that cancer is specific; Leitch contends that the idea of specificity is merely a "notion" destined to be "finally broken"; Brand believes that mechanical and chemical irritants can be accepted as merely "predisposents." The protozoal origin of cancer briefly discussed in my earlier paper is possibly not disproved, surely unproved; J. Jackson Clarke (Protists and Diseases, London, 1922) attributes sarcoma to protists.

REFLEX SPASM OF THE PYLORUS AND ITS RELATION TO DISEASES OF THE DIGESTIVE ORGANS*

WALTER HUGHSON, M.D.

BALTIMORE

There is probably no field in the whole subject of medicine about which we have so little absolute knowledge as that of the neurology of the gastro-intestinal tract. Nor is there any field of investigation to which more time and effort have been devoted in the endeavor to clear up the many perplexing problems which it presents. The complicated nervous mechanism involved—the very complexity of the structures themselves, with their apparent autonomous activity—makes the approach to the subject bewildering in the extreme. Yet derangement of digestive function in one form or another is probably one of the most common of all diseases. Our therapeutic efforts, whether medical or surgical, are largely symptomatic; even when they are distinctly rational they are often unsatisfactory. Drugs that may have a special effect on a given nerve are administered; but we now know that these nerves may act in an entirely different way under such different circumstances as varying degrees of stimulus, etc. Consequently, the effect of the drug may not be at all the one sought. Surgical procedures are adopted to meet various contingencies; as a result the normal relations of the different parts are completely changed, and the patient is left to adjust his digestive apparatus to an entirely new physiologic process. Such a condition has persisted, undoubtedly because of the fact that the stomach and intestine have remarkable powers of adaptation, and although far from normal function is obtained, the human organism can maintain itself in a certain amount of comfort in spite of these rather unsound procedures. Indeed, many individuals are cured of disease by permanent gastro-enterostomy, an operation which from a physiologic standpoint could hardly be less rational. There is no reason why we should accept this situation, or regard the problems of the alimentary tract as impossible of solution. Our knowledge in regard to treatment and etiology is by no means comparable to the advances made in the actual recognition of disease. This is obviously an anomalous situation in which to be placed. For, with diagnosis approaching a high state of perfection, our real understanding of the actual pathology involved has progressed very slowly.

One phase of this subject presents many interesting and intricate problems, namely, the reflex activity of the pyloric sphincter. No part

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of the alimentary canal is so subject to derangement of normal function from influences either immediately adjacent or quite remote, and probably no portion of the digestive tube bears so close a relation to all diseases of the stomach and duodenum as does the pylorus itself. Indeed, it is far from improbable that much of the actual pathology of the stomach is secondary to changes in the normal functioning of the stomach outlet. With this idea as a basis, various investigations have been undertaken in order to reach, if possible, a somewhat clearer understanding of a few of the factors involved in abnormal pyloric activity.

Many difficulties present themselves in an experimental study of this kind. Little, if any, analogy can be drawn between conditions found in the human organism as a result of disease and the acute conditions produced on experimental animals. The production of any chronic disease of the alimentary tract in an animal is almost impossible; efforts have been made, however, in the course of these experiments to bring about conditions simulating as nearly as possible those found in the human being, while the interpretation of these results was never made in the course of any single acute physiologic experiment.

A brief review of the anatomy of the pyloric portion of the stomach and of the current physiologic theories of its activity may be of interest. Grossly, that portion of the stomach to which we shall devote most of our attention begins at the incisura angularis; this forms, as it were, the entrance of the pyloric vestibule, which in turn is limited distally by the sulcus intermedius. The latter landmark, together with the pyloric sphincter, bounds the pyloric canal. In regard to the actual musculature of the stomach wall at this point, there is a general piling up or thickening of both the longitudinal and circular fibers, the latter making up the strong pyloric sphincter at the duodenopyloric junction. Without regard to function for the moment, suffice it to say that the extrinsic nerve supply to the stomach is, of course, twofold—namely, the sympathetic and the vagus. The former is derived for the most part from the celiac ganglion and distributed to the pylorus by the various arteries; one branch, the gastrohepatic, however, joins the vagus at the cardia and is distributed along with the gastric branches of the vagus itself to the anterior and posterior surfaces of the stomach and pylorus. These branches of the vagus therefore carry both sympathetic and vagal fibers; as they fan out from the lesser curvature they supply very definite areas of the stomach, the terminal branch extending to but never beyond the pyloric sphincter.[1] The intrinsic plexuses are practically the same in the stomach as they are in the rest of the intestinal tract. Although they are given a definite position in textbooks of anatomy, the radiolo-

1. Latarjet, A.: Résection des Nerfs de l'estomac; Technique Opératoire; Résultats Cliniques, Bull. de l'Acad. de méd. **87**:681-691, 1922.

gists have shown most conclusively that there is a marked type variation, if not an individual one, in the actual location and shape of the stomach.

The physiology of the antrum pylori, to use a term discarded by Cannon,[2] and of the pylorus itself is a matter of the greatest complexity. Cannon's extensive studies on the acid control of the stomach present a theory of the greatest interest, although the acid control is now regarded as one possible factor among many, and indeed only as an explanation in the normal stomach by Cannon. It is now generally agreed that there is a much more definite relation between the muscular activity of the stomach and the opening of the pylorus than there is between the opening of the sphincter and the gastric contents. In short, the antrum is definitely an organ of special motility.[3] Wheelon and Thomas [4] have shown graphically a rhythmic motility of the antrum, the cycle consisting of phases of contraction, relaxation, quiescence and inhibition, and the pyloric portion showing similar phenomena always following the antral contraction. These authors further maintain that, if acid is a factor, it must control the motility of the entire stomach; for, like the stomach proper, the sphincter has two types of motility, namely, active rhythmic contraction and tone waves. The tonicity is high following ingestion of food and peritoneal irritation. Alvarez [5] feels that the opening and closing of the pylorus "depends in a large measure on mechanical factors, that is, differences in the gradient and tone and irritability between the stomach and duodenum."

The function of the nerves, whether intrinsic or extrinsic, of the stomach is in an even more unsettled state so far as absolute knowledge is concerned. Briefly, the evidence in favor of an intrinsic reflex arc has more of a physiologic than an anatomic basis, for peristalsis continues after complete separation from all extrinsic supply. If the nerves of the plexuses of Meissner and Auerbach are anything more than a network, and this we would certainly expect from the definite indication of their reflex activity, then R. Muller's [6] two types of ganglion cells described in the myenteric plexus may have some significance, for a

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2. Cannon, W. B.: The Mechanical Factors of Digestion, Longmans Green & Co., 1911.

3. Luckhardt, A. B.; Phillips, H. T., and Carlson, A. J.: Contributions to the Physiology of the Stomach. LI. The Control of the Pylorus, Am. J. Physiol. **50**:57-66 (Oct.) 1919.

4. Wheelon, H., and Thomas, J. E.: Observations on the Motility of the Antrum and the Relation of Rhythmic Activity of the Pyloric Sphincter to that of the Antrum, J. Lab. & Clin. Med. **6**:124-143 (Dec.) 1920; Rhythmicity of the Pyloric Sphincter, Am. J. Physiol. **54**:460 (Jan.) 1921.

5. Alvarez, W. C.: The Mechanics of the Digestive Tract, Paul B. Hoeber, New York, 1922.

6. Muller, L. R.: Die Darminnervation, Deutsch. Arch. f. klin. Med. **105**: 1-43, 1912.

reflex demands both receptive and excitor elements. The fact that muscle cells, stripped of all nerve fibers, undergo rhythmic contraction in Locke's solution would hardly appear to have any bearing on the subject, although the myogenic theory of peristalsis is an important one.

Observations on the effect of vagus and splanchnic stimulation offer little more definite information. All degrees of specificity of function are assigned to the vagus and sympathetics. Vagus stimulation causes eventually an increase both of tonus and amplitude of rhythmic waves, while stimulation of the splanchnic causes diminished tonus and weakened rhythmic contraction. Peristalsis continues, however, after complete separation from all extrinsic supply, showing that the contractions are simply modified by the vagus and sympathetics. Many authors ascribe pure function to these two sets of nerves, that is, to the splanchnic inhibition and to the vagus excitation of contraction.[7] Wheelon and Thomas [8] have shown that, depending on the strength of stimulation, activation or inhibition may be obtained from either nerve. These authors have also shown that, with the same stimulus, the response of a given nerve will vary in a perfectly definite number of cases. These observations were all made graphically. In a series of experiments they have obtained the following results with the same degree of stimulus:

Vagus: 89 per cent. motor; 11 per cent. inhibition. Splanchnics: 63 per cent. motor; 37 per cent. inhibition.

In addition to the actual response obtained by nerve stimulation, Wheelon and Thomas noted blood pressure changes during their experiments. A motor response to splanchnic stimulation was always associated with a fall in blood pressure, while inhibition was followed by a rise. Cannon had noticed a loss of tone following the administration of epinephrin, and Shipley and Blackfan [9] have corroborated this in observations made on embryos while they were studying Pirie's theory of congenital hypertrophic stenosis of the pylorus.

These data are reviewed, not with the idea that any great light will be shed on the subject, but more for the purpose of demonstrating to a greater extent its perplexity.

Experimentally spasm of the pylorus has been studied by many investigators and, in addition, much attention has been devoted to the condition by clinical observers. Chemical and mechanical stimulation

7. Koennecke, W.: Experimentelle Innervationsstörungen am Magen und Darm, Klin. Wchnschr. **1**:1262 (June 17) 1922.

8. Wheelon, H., and Thomas, J. E.: The Nervous Control of the Pyloric Sphincter, J. Lab. & Clin. Med. **7**:375 (April) 1922.

9. Shipley, P. G., and Blackfan, K. D.: The Pharmacological Action of Adrenalin on the Sphincter Pylori of the Foetus, Bull. Johns Hopkins Hosp. **33**:159 (May) 1922.

of the mucous membrane does not particularly concern us; Carlson,[10] Cannon and many others have studied this particular phase. But spasm of the pylorus resulting from extra-gastric stimuli is of immediate importance, particularly from a surgical point of view. Here, again, we have many sources from which to obtain definite data. Contraction of the pylorus and of the whole gastro-intestinal tract after stimulation of any peripheral sensory nerve is a matter of general knowledge. Hotz [11] has shown that such stimulation leads to intestinal movements and lays the path in the spinal cord and splanchnics, while Lehmann [12] demonstrated the fact that intestinal movements may be stopped by stimulation of the central end of the hypogastric, splanchnic and vagus nerves. Sciatic stimulation causes an arrest of the pendulum and, when it is prolonged, of the peristaltic movements of the intestine. This does not happen if the splanchnics and cord are divided, and therefore Lehmann concludes that the center must be in the medulla and the efferent path in the splanchnics. Barber and Stewart,[13] in a series of papers, have shown experimentally that trauma, such as crushing, of various organs has a marked stimulating effect on the activity of the stomach and pylorus. This hypermotility is shown by increased peristalsis of the stomach and the pyloric canal and sphincter, the latter manifesting itself in the form of a definite pylorospasm. With acute experiments they were able to demonstrate by traumatization of the gallbladder, duodenum and appendix, a diffuse pylorospasm with fundic relaxation resembling a pylorofundic intussusception. They have also observed these reflex phenomena after irritation of the parietal and visceral peritoneum, and feel that the motor functions of the stomach may be stimulated or depressed according to the intensity of the irritation.

Clinically, there are many reports dealing with the subject; Barber [14] again details observations made in the open surgical abdomen, showing this hypermotility for gallbladder disease in 61.5 per cent., for duodenal trauma in 7 per cent., and for appendix disease in 100 per cent. of all cases studied in this way. Finding the pylorus tightly contracted imme-

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10. Carlson, A. J.: Contributions to the Physiology of the Stomach. V. The Influence of Stimulation of the Gastric Mucosa on the Contractions of the Empty Stomach (Hunger Contractions) in Man. VI. A Study of the Mechanisms of the Hunger Contractions of the Empty Stomach by Experiments on Dogs, Am. J. Physiol. **32**:245-263, 369-388, 1913.

11. Hotz, G.: Beiträge zur Pathologie der Darmbewegungen, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **20**:257, 1909.

12. Von Lehmann, A.: Studien über Reflektorische Darmbewegungen beim Hunde, Arch. f. d. ges. Physiol. **149**:413-433, 1912.

13. Barber, W. H., and Stewart, G. D.: Further Observations upon Reflex Gastric Hypermotility, Proceedings Soc. Exper. Biol. & Med. **17**:155, 1919-1920.

14. Barber, W. H.: Gas and the Motility of the Surgical Stomach, Ann. Surg. **69**:271-277, 1919.

diately after the abdomen is opened is a common experience for every abdominal surgeon; the subsequent relaxation either results from prolonged manipulation of the stomach or from actual stretching of the sphincter.

Spasm of the pylorus is the basis of a large number of the roentgen-ray diagnoses of pathologic conditions of the gastro-intestinal tract, and much light has naturally been thrown on our knowledge of its relation to abdominal disease by the radiologists.

From a purely physical, clinical standpoint we have many interesting phases of the subject to consider. We may accept Haynes'[15] definition as being conclusive: "By pyloric spasm is meant a spasmodic contraction of the pyloric ring, the pyloric canal or both . . . it may be either brief with irregular recurrences or last a long time and be almost continuous." What then are the symptomatic manifestations of this pyloric spasm? Haynes lists the chief symptoms as colicky and cramp-like pain in the epigastrium reflected along the splanchnic nerves to the back, eructation of gas or some fluid, vomiting, late pain or hunger pain relieved by the ingestion of food. Saloz and Moppert[16] ascribe to pyloric spasm an important part in the symptomatology of ulcers. They feel that of all the phenomena only this late pain has a clinical individuality and an importance sufficient to elevate it to a definite pathologic condition. It is always the same in different individuals, and is affected little if any by the personal equation. Hardt, with a balloon and tube, studied contraction and chemistry; he found that pain was always synchronous with contractions of the stomach. Muscular contractions tend to stop this after gastro-enterostomy, and pain disappears promptly. If this idea of spasm as the principal factor in the cause of pain is generally admitted in lesions of or near the pylorus, might it not be the same when a lesion is situated at a distance from the opening? Saloz and Moppert conclude that every obstacle to the normal evacuation of the stomach contents expresses itself clinically by late pain, and that, though this obstacle may be organic, it is much more often functional.

In reviewing the factors ascribed as having an etiological bearing on pylorospasm one is immediately confronted with an imposing array of disease. Brown[17] lists eleven causes for spasm; among them are non-bacteria toxic disturbances, also bacterial disease aside from infections within the peritoneal cavity, and central nervous system diseases. He then enumerates seriatim all the intra-abdominal and juxta-abdominal

15. Haynes, I. S.: The Significance of Pyloric Spasm, Am. J. Surg. **29**: 425-430, 1915.

16. Saloz, C., and Moppert, G. G.: Le Spasm Pylorique, Arch. d. mal. de l'app. digestif, **13**:97-133 (Feb.) 1923.

17. Brown, A. G.: Diagnosis of Certain "Stomach Cases," Southern M. J. **7**:617, 1914.

disorders. Raymond [18] describes three main groups: first, the local type with actual disease of the stomach or duodenum including ulcerations, new growth and infections; second, the true reflex type resulting from the disease of the gallbladder, kidney, pancreas and appendix, as well as from causes of a general nature, such as abnormal conditions of the central nervous system, "spasmophiles," including cases resulting from all types of excess. Finney and Friedenwald [19] divide their cases into three groups; namely, neurotic, irritative and reflex. The first they regard as unusual. Lerche [20] explained that one of his cases was the result of intrathoracic irritation of the vagus. Held and Roemer [21] consider intragastric and extragastric factors, the latter including all conditions whether organic, toxic or the result of drugs.

It is certain that the great majority of cases of pylorospasm are directly attributable to pathologic conditions either of the stomach or of some one of the abdominal viscera. In a roentgen-ray study of sixty-one patients with gastric or duodenal ulcer, Saloz and Moppert found six-hour retentions as follows:

Pyloric ulcer, 89 per cent.; duodenal ulcer, 27 per cent. Parapyloric ulcer, 53 per cent.; ulcer of the lesser curvature, 59 per cent.

These cases were all confirmed at operation. In a group of thirty-two patients with gastric ulcer operated on in the Johns Hopkins Hospital, definite symptoms of pylorospasm were noted clinically; at operation, the lesion was found in the immediate neighborhood of the pylorus, though not actually involving it. An illustrative case is the following:

REPORT OF CASE

CASE 1.—L. R., a colored man, aged 36, had pain and vomiting for three months, with gastric hemorrhage occurring ten days before admission. The vomiting was so severe that the patient was greatly dehydrated. The blood chlorids amounted to 370 mg. The roentgen ray showed an ulcer of the lesser curvature. The emptying time of the stomach was 6.5 hours. At operation, a large saddle ulcer was found; this was at least 5 cm. from the pylorus, and yet the chief symptom for a period of at least three months was vomiting.

Appendicitis, whether it is acute, subacute or chronic is almost invariably associated with some evident reflex pylorospasm which may be persistent or intermittent.

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18. Raymond, M. F.: Le Spasme du Pylore (Pylorespasme), Presse méd. **28**:273, 1920.

19. Finney, J. M. T., and Friedenwald, J.: Pylorospasm in Adults: Its Medical and Surgical Treatment, Am. J. M. Sc. **162**:469 (Oct.) 1921.

20. Lerche, Wm.: Spastic Tumor of the Pyloric Canal and Other Spastic Conditions of the Stomach: Their Surgical Treatment, Surg. Gynec. & Obst. **18**:358, 1914.

21. Held, I. W., and Roemer, J.: Gastrospasm, Am. J. M. Sc. **164**:188 (Aug.) 1922.

In an analysis of eighty-three cases of appendicitis diagnosed chronic in the Johns Hopkins Hospital, eighteen patients were found to be practically normal at operation and on pathologic examination, although clinical evidence of pylorospasm was present. Eight cases were associated with other abdominal disease, such as gallbladder infections, peptic ulcers or pelvic disorders, which were probably responsible for the symptoms. In the remaining fifty-seven, the diagnosis was confirmed at operation and by the pathologist. All of the patients gave an intermittent history of pylorospasm. The more acute the condition becomes the more marked are the pyloric symptoms.

Aaron [22] was able to produce pyloric spasm by pressing the appendix region in a patient with an acute appendicitis. A patient recently observed experienced marked pain in the epigastrium when the appendix, which was palpable, was rolled under the fingers. Operation revealed a definite subacute inflammation of the appendix and relieved completely the vomiting attacks, which had persisted for two years. Galbladder disease is so uniformly associated clinically and radiographically with pylorospasm that there is little need of discussion. Indeed, there are very few pathologic conditions of the peritoneal cavity, pelvis or retroperitoneal region which are not at some time in their course associated with spasm of the pylorus; this is evidenced by the accepted symptomatology. This is certainly true as regards inflammatory processes in which the attacks are usually initiated by epigastric pain in addition to local pain, nausea and vomiting.

In spite of the fact that so many skilful investigators had studied the problem of pyloric obstruction, it seemed possible that a general review of the subject from an experimental standpoint might bring to light a few facts of a definite practical interest. With this idea in mind, a study of the motility of the gastro-intestinal tract in laboratory animals (dogs have been used throughout) was undertaken about a year and a half ago. Our observations on normal animals were so at variance with published standards that it very soon became evident that we would have to establish a normal of our own. This involved a study of a considerable number of animals under constant experimental conditions which we arbitrarily chose as representing the normal motor physiology of the stomach. Following a change in procedure early in our work, the experimental conditions have at all times been constant and the results, in so motley a group of experimental animals as stock dogs, surprisingly uniform.

Dogs, in general, were selected of a given size, variations in weight being only a matter of one or two kilograms. In other words, the

22. Aaron, C. D.: Chronic Appendicitis, Pylorospasm and Duodenal Ulcer, J. A. M. A. **64**:1845 (May 29) 1915.

difference was never enough to indicate any marked discrepancy in the size of the stomach and intestine. And so far as possible animals in good physical condition were used. The animals were fed the same kennel meal, consisting of prepared dogbread and meat with bones, at 4 p. m. the afternoon before examination. All fluoroscopic studies were started at 9 o'clock in the morning. In the intervening time the dogs were allowed water ad libitum, but nothing else. In none of the normals was any food residue observed under the fluoroscope, seventeen hours after feeding. From 250 to 300 c.c. of fluid was found to be the quantity that gave the stomach a moderate degree of distention. One and a half ounces (42.52 gm.) barium sulphate mixed in the water was used as the opaque medium. The animals were all fed by means of a stomach tube, which was passed through a special mouth gag. Before the tube was passed the dogs were tied down on their backs. This was always simpler and quicker for the first examination, but when several examinations were made the dogs could soon be managed simply by having them held between the assistant's knees. An effort was always made to remove any air that was present in the stomach. For the first six experiments the dogs were tied down on their backs during the fluoroscopic examination, but this was soon found to be unsatisfactory. In addition to making the animal restless and excitable, as well as to causing pain and thus introducing an extraneous factor of considerable importance, according to most observers, the normal outline of the stomach was definitely distorted owing to its being hung, as it were, over the dog's vertebral column. All subsequent studies were made, therefore, by simply having the dog lie down on its stomach without any artificial means of restraint other than holding its head. Previous to the examination, the dogs were allowed to become accustomed to the dark room and the noise of the fluoroscopic machine. With the adoption of this routine, the difficulties of examination were reduced to an absolute minimum. Fluoroscopic examinations were made immediately after the barium suspension was given and at frequent intervals after it (usually every fifteen or twenty minutes) until the stomach was empty. Whenever any point of particular interest was observed, a plate was made as a permanent record. Our technic for this was simple and quite satisfactory. An intensifying screen was always kept loaded, and when the plate was to be exposed the screen was simply held over the dog's back and a flash exposure made. This flash of necessity has to be very rapid on account of the speed of the animal's respiratory movements.

Several interesting observations of a general nature were made in addition to the detailed data which will be given below. Although we realized that our studies were made under different conditions from most of those previously made—that is, our opaque meal was simply a water suspension and consequently no chemical factors were involved—the

greater constancy of experimental conditions obtained in this way over the method of allowing the dog to eat food in which barium had been mixed, seemed a very distinct advantage; in addition, the routine was under our absolute control at all times. In all examinations the general size and shape of the stomach and its individual parts was carefully noted, in addition to its motor activity as indicated by the size and frequency of the contraction waves. The condition of the plyorus could be studied with great accuracy by noting the amount of the opaque mass discharged into the duodenum by each contraction wave, the size of the antrum pylori, the shape of the duodenal cap and, everything else being equal, the actual emptying time of the stomach.

Very early in our studies we became convinced of a fact which is at variance with previous observations. The only effect that excitement, anger or pain had on the emptying of the stomach was to hasten it. Emotional states may manifest themselves differently in individual cases and in different species, of course; but in this series, the effect described was a distinctly uniform one. Ordinarily, in the animals that permitted the passage of the stomach tube without undue struggling, immediate examination failed to show any of the barium in the duodenum; in those that were vicious or struggled violently either from anger or pain, immediate examination invariably showed the duodenum already filled, and frequently the mass was well down in the small intestine. This increased activity persisted usually throughout the period of observation.

In the study of normals it was thought that examinations repeated on the same dog in order to check possible variations from day to day would be of more real value than single examinations on a large number of animals. Twenty-six animals were observed in this way for a total of forty-one complete fluoroscopic studies. The daily variations were surprisingly small. In Dog 8, for instance, examination carried out on four separate days showed emptying times of 4, 3, 3.5 and 3.5 hours; others on whom two examinations were made were as follows: 2, 2.5; 4, 4; 4, 3.5; 4, 3.5; 2, 2.5; 2, 1.5. The only marked variation noted was in Dog 13 in which the emptying time on two examinations was 6 and 3.5 hours. For all examinations, an average emptying time of 3.4 hours was obtained, with low and high extremes of 1.5 and 6 hours; there were two instances each of such figures.

After having arrived at a satisfactory normal, our effort was directed towards producing conditions which would in some way delay the emptying time without decreasing the actual motor activity of the stomach. Practically all experimental data dealing with this subject have to do with acute traumatization of various abdominal viscera and observation of the immediate effect on the pylorus. Although they confirm clinical studies, the two conditions are in no sense the same. This

point cannot be emphasized too strongly, and represents an error into which investigators of pathologic physiology are prone to fall. The acute physiologic experiment cannot be taken as the basis of an explanation of clinical pathology. Chronic irritation of the abdominal organs in a dog, as has already been stated, is difficult to obtain, largely because of the speed with which the animal's peritoneum takes care of an average amount of infection. However, the result of various traumatic procedures produced an effect which was fairly comparable to an acute clinical process with its ensuing subsidence. One very satisfactory method adopted was that of making a linear incision the length of the dog's appendix with the actual cautery, no great care being taken to avoid traumatizing the neighboring peritoneum. The effect of this procedure was apparent for approximately two weeks. Large and small intestinal anastomoses proved equally satisfactory, and it was soon found that, in any animal whose peritoneal surface had been traumatized in the course of some surgical procedure, the emptying time of the stomach was markedly delayed according to the severity of the treatment. In addition to the use of our own experimental animals, those which had been used in the students' course in operative surgery were studied. These operations consisted of splenectomies, appendectomies, intestinal suture and cholecystectomies, resulting in a varying degree of peritoneal irritation. Simple laparotomy with opening and closing of the peritoneal cavity had also an appreciable effect. Twenty animals were studied in this way, several having had their normal established before operation. These showed for all conditions an average emptying time of 5.7 hours, or nearly 2.5 hours above normal. The longest period of emptying was seven hours with the stomach still discharging and the shortest two hours. In only two instances was the emptying time less than five hours, while but six were under six hours. In only a few cases did the effect last more than two weeks. The first fluoroscopic examination was made twenty-four hours after operation and on subsequent days thereafter. Motility of the stomach, as measured by the frequency and strength of contraction waves, was carefully noted and found to be unaffected, except when there developed a definite general peritonitis following operation. No animals in this group had been subjected to stomach operations. Simple ether anesthesia for one hour failed to produce any appreciable delay in the emptying time, nor did the hypodermic injection of ½ grain (0.0324 gm.) of morphin have more than a temporary effect.

When an attempt was made to analyze this series of experiments it seemed difficult to attribute the uniform effect obtained to traumatization of any specific organ. In other words, might there not be one structure, irritation of which would cause a reflex spasm of the pylorus? This immediately resolved itself into ascribing the afferent path of the reflex

as coming from the peritoneum itself, rather than from any particular viscus. Obviously, no intra-abdominal operation can be performed without traumatization of peritoneal surfaces, nor can any inflammation, whether it is acute, subacute or chronic, be present without involving the organ's peritoneal covering. Although actual proof is difficult to make, the facts described above and our knowledge of the pathology of various abdominal affections lend strong support to such an hypothesis.

Dog 7 is illustrative of the cases in this series.

TABLE 1.—*Experimental Findings (Dog 7)*

Date	Procedures and Findings
Feb. 6, 1924	Emptying time, 3 hours
Feb. 8, 1924	Linear incision with cautery of appendix and immediate suture; ether anesthesia
Feb. 9, 1924	Emptying time, 5.5 hours
Feb. 11, 1924	Emptying time, 6 hours
Feb. 20, 1924	Emptying time, 5 hours
March 4, 1924	Emptying time, 4 hours

Although the results of the fluoroscopic examinations tabulated above were quite conclusive to the actual observers, the interpretation of normal stomach motility might well be questioned without graphic or other evidence to support it. If the pylorus alone was held responsible for the delay in emptying caused by peritoneal traumatization, extirpation of the sphincter should result in normal discharge, if not an actual increase in speed. Such a study was therefore made with adequate control observations on stomach operations performed elsewhere than at the pylorus, in order to obviate the possibility of hypermotility resulting from the operative procedure itself. The results obtained in this series were very striking.

Several methods of pylorectomy are available, the Finney pyloroplasty, the Heberer-Finney gastroduodenostomy, and a new type of gastroduodenostomy used in several of this series of experimental animals. Following these operations the emptying time was, in every instance but one, materially shortened; and the effect persisted over periods of time from two to three months, or rather, as long as the animals were under observation. The one exception was an animal on which a Heberer-Finney operation had been performed; the emptying time the day after the operation was five hours. This was undoubtedly due to postoperative edema of the inverted duodenal stump, which temporarily occluded the new stoma, as the stomach showed active peristalsis and apparent obstruction to emptying. All subsequent observations on this animal covering a period of two months showed an emptying time of two hours or less.

In eleven such studies, the average time for complete evacuation of barium suspension was 1.9 hours; the longest elapsed time was five hours, as mentioned above, and the shortest 0.5 hours. All but the five-hour observations were under two hours. The speed of emptying bore a distinct relation to the amount of the pyloric antrum resected. For example, in Dog 29 practically the whole antral portion was removed, a gastroduodenostomy performed, and the subsequent emptying time was always less than one hour. The final examination made seven weeks after operation showed an empty stomach in fifteen minutes. Incidentally, this animal was extremely excitable and difficult to manage.

The details of results obtained in some of these animals are given in Table 2.

TABLE 2.—*Experimental Findings*

	Date	Procedures and Findings
Dog 9	Feb. 11, 1924	Emptying time, 4 hours
Dog 9	Feb. 13, 1924	Emptying time, 4 hours
Dog 9	Feb. 14, 1924	Operation—Gastroduodenostomy. Ether anesthesia
Dog 9	Feb. 15, 1924	Emptying time, 2 hours
Dog 9	Feb. 18, 1924	Emptying time, 1 hour 55 minutes
Dog 15	Feb. 27, 1924	Emptying time, 4 hours 45 minutes
Dog 15	Feb. 29, 1924	Emptying time, 4 hours
Dog 15	March 6, 1924	Operation—Heberer-Finney
Dog 15	March 7, 1924	Emptying time, 5 hours
Dog 15	March 10, 1924	Emptying time, 2 hours
Dog 15	March 14, 1924	Emptying time, 1 hour 45 minutes
Dog 15	May 5, 1924	Emptying time, 2 hours
Dog 17	Feb. 27, 1924	Emptying time, 4 hours 15 minutes
Dog 17	Feb. 29, 1924	Emptying time, 4 hours
Dog 17	March 12, 1924	Gastroduodenostomy
Dog 17	March 14, 1924	Emptying time, 2 hours 30 minutes

In a series of six class dogs, in which Finney pyloroplasties had been done, the emptying time proved to be somewhat delayed, averaging 4.9 hours. This result calls for two possible explanations. The remaining portion of the pyloric ring may have so contracted as partially to occlude the new lumen; or, what seems more probable, the operative technic may have been at fault. The striking and conclusive fact obtained from this series, however, was that with total extirpation of the pylorus the delay in the emptying time subsequent to all operative procedures in the abdomen, as illustrated above, was entirely obviated. In other words, the reflex mechanism involves the pyloric sphincter alone. Additional evidence in support of this fact is brought out by a second operation performed on Dog 15. Here, the appendix was traumatized as in Dog 8 by cautery incision. The comparative results are given in Table 3; it should be remembered that a pylorectomy had been performed on Dog 15.

Two days later Dog 15 died of a general peritonitis; this indicates that at the time of examination the peritoneal irritation must have been severe. Many other facts of a confirmatory nature were brought out in the course of this study; but the cases were isolated ones, and hence have not been incorporated in the final results.

COMMENT

In the light of the experimental and clinical data reviewed above and the experimental results herewith reported, a somewhat clearer idea of the mechanism of the production of pylorospasm and its relationship to the pathology of the abdominal viscera can be gained. There can be little doubt that influences outside the abdominal cavity, such as those enumerated by Brown, may also produce hyperactivity of the pyloric sphincter; but certainly the great majority of conditions causing epigastric pain, nausea and subsequent vomiting, whether of an actual

TABLE 3.—*Experimental Findings*

Procedure	Dog 7	Dog 15
Emptying time before operation....	3 hours	2 hours
Operation—Cautery incision of appendix		
Emptying time after operation.....	5.5 hours	1 hour 55 minutes

inflammatory nature or not, are found in the abdominal cavity or directly adjacent to it. And in every instance, the peritoneal covering of the viscus must of necessity be involved by the disease process. If the peritoneum itself can be regarded as the receptor mechanism of the reflex arc, we are in a position to explain symptoms of many hitherto obscure conditions. Acute inflammatory or ulcerative processes are obviously responsible for the classical symptoms presented, each organ being characterized in its symptom complex by a few manifestations resulting from its special location, while the gastric disturbances are common to all. Subacute conditions are equally easy to understand. The chronic cases and those in which no apparent pathology exists, however, present a much more difficult problem. Frequently, laparotomy is performed and the only condition found to explain a train of symptoms of long standing may be a few filmy adhesions between the gallbladder and duodenum, or the appendix and the cecum. This is definite evidence that an inflammatory process has at some time involved one or the other structure, and that irritation, however mild it may be, is still continuing, for these adhesions must continue to contract for long periods of time. Going a step further, there exists the type of case in which the most skilful operator fails to find any pathology whatever, and the patient undergoes repeated operations in the effort to gain relief. Finally, in

the classification of Finney and Friedenwald, there exists a purely neurotic type of pylorospasm. Is it not possible that in the abdominal cavity we may have hyperactive reflexes just as well as of any other part of the body? The "spasmophiles" of Raymond, reacting strenuously to the slightest stimulus, must furnish us the explanation for this large group of cases. Provided the position of the stomach is not such as to offer mechanical difficulties to emptying, and even such a condition might well be secondary, there seems little doubt that there must be some organic basis for all functional derangements of the pyloric sphincter.

Finney has long been an advocate of operative treatment in cases of pylorospasm, and with Friedenwald has reported a considerable number of such cases treated successfully by pyloroplasty. Haynes has stated: "While there are so many conditions that may produce pyloric spasm there are only a few which do." This is probably far from being accurate and might better be expressed by saying that many more conditions than we realize do produce spasm of the pylorus. While surgically we are entirely unable to avoid peritoneal irritation of some kind, we are exposing every patient with an intact pylorus to the possibility of a reflex spasm with every abdominal operation. Just as it is impossible to avoid the production of adhesions, so it is beyond the present power of surgery to resolve adhesions already formed. Constitutional measures having failed, the only recourse is to surgery directed towards the active seat of trouble, which is the pyloric sphincter. Within the month, Strauss [23] has reported the results of an experimental and clinical study on longitudinal resection of the lesser curvature, with resection of the pyloric sphincter for gastric ulcer. His experimental results are quite in accord with those reported above, although his operation at the pylorus was more of the nature of a plastic procedure. He extirpated a triangular piece of muscle on the anterior and posterior surfaces of the pylorus somewhat after the manner of the Ramstedt operation. Following such a procedure, resection of the lesser curvature, as for an ulcer of that part of the stomach, never caused any delay in the emptying time. In addition to furnishing experimental data, Strauss reports a considerable series of clinical cases.

The final relation between gastric ulcer and pylorospasm is one of very great importance undoubtedly. Efforts to produce ulcers experimentally have never met with any great degree of success; when produced, they heal so promptly that comparison with clinical cases is difficult. With ulcer there is a tendency, as shown by cases analyzed in

23. Strauss, A. A.: Longitudinal Resection of the Lesser Curvature with Resection of Pyloric Sphincter for Gastric Ulcer, J. A. M. A. **82**:1765 (May 31) 1924.

this clinic and by Saloz and Moppert, for pylorospasm to be present. Which is the cause and which the effect. The latter authors believe the pylorospasm to be primary; they state, in effect, that when chronic spasm of the pylorus is produced, chronic experimental ulcer will be possible.

CONCLUSIONS

1. Three and four-tenths hours has been established by fluoroscopic examination as the normal emptying time of a dog's stomach with conditions under absolute experimental control as to size, weight, and method of administration of the opaque meal consisting of barium sulphate and water in constant proportion.

2. Traumatization of any abdominal viscus in dogs by surgical procedure increases this emptying time approximately 67 per cent. for a period of about two weeks.

3. The motility of the stomach is unaffected by this traumatization except that the speed of contraction waves is increased.

4. The hypothesis is advanced that spasm of the pylorus resulting from disease either within or adjacent to the abdominal cavity is solely due to irritation of the peritoneal surface.

A REVIEW OF UROLOGIC SURGERY

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TRANSPLANTED MUSCLE IN RESECTION OF THE KIDNEY

Ciminata [1] covered the raw surface of the renal parenchyma of dogs with a strip of muscle to prevent bleeding after resection of a portion of the kidney. Portions of the surface of the kidney were removed or one of the renal poles resected; muscle tissue was sutured over the raw surface. This underwent gradual degeneration and was replaced by connective tissue. The cut surface of the kidney healed quickly and without bleeding. In none of the experiments was regeneration of the transplanted muscle noted.

[ED. NOTE.—It has long been known that the use of transplanted muscle tissue as a hemostatic is one of the most satisfactory methods of controlling bleeding from surfaces, especially in operations on the brain. Muscle tissue regenerates poorly at best, and as a transplant it usually atrophies and is gradually replaced by fibroblastic tissue. The use of muscle tissue to cover raw bleeding surfaces after resection of the kidney is therefore logical and based on surgical principles already established in other fields. Similar studies might well be carried out on the control of bleeding from the raw surface of the liver.]

EXPERIMENTAL NEPHROTOMY

Carson and Goldstein [2] performed experimental nephrotomy in a series of cases. No clamps were used on the renal vessels. The kidney

1. Ciminata, Anton: Ueber die Resorption der Muskeltamponade bei Nierenresektion, Ztschr. f. urol. Chir. **16**:37-47, 1924.

2. Carson, W. J., and Goldstein, A. E.: Experimental Nephrotomies, South. M. J. **17**:786-794 (Oct.) 1924.

was incised from pole to pole with a scalpel in most cases. The cut surfaces of the kidney were then approximated and held together by light pressure until bleeding ceased. The bleeding time varied from two to seven minutes in thirteen cases and was sixty-five minutes in one case. In no case was there any complication such as postoperative hemorrhage, uremia, infection, stone formation or fistula. No sutures were used in the kidney, and the incisions in the body wall were closed without drainage. In thirteen of the fourteen cases, nephrectomy was performed from one to 170 days later. Death occurred in two cases, one from pneumonia and one from pelvic peritonitis. The method employed reduced postoperative complication to a minimum, and a histologic study demonstrated minimal destruction of renal tissue.

A METHOD OF CLOSURE

Escat,[3] in order to effect an exact adaptation of the muscles which are cut in the oblique lumbar incision, and thereby to prevent postoperative hernias, recommended that the deeper layers be fixed with catgut sutures before the muscles are divided. This will tend to diminish the retraction of the muscle fibers.

RENAL ANOMALIES

Kretschmer [4] asserts that anomalies of the kidney are of two kinds: supernumerary, or three separate kidneys, each with a separate vascular supply, and one kidney, which may be the consequence either of the unilateral fusion of two kidneys or the congenital absence of one. Careful distinction should be made between unilateral fused kidney and congenital absence of one kidney. In unilateral fused kidney the fusion may be so complete that the resulting compound organ closely resembles in shape and general appearance a single kidney with complete ureteric duplication. Solitary kidney should always be interpreted as one kidney with its pelvis and ureter. Unilateral fused kidney should always indicate cases in which the renal mass consists of both right and left kidneys. Stein reviewed fifty-eight cases of unilateral fused kidney in 1916. Kretschmer has compiled twenty-eight cases since the publication of Stein's article. Forty-seven of Stein's patients were males. Of Kretschmer's twenty-nine patients, eighteen were males and six females; in five cases the sex was not mentioned. In sixteen cases the mass was on the right, and in ten on the left; in three cases the side was not

3. Escat: Incision et restauration de la paroi lombo-abdominale dans les opérations sur le rein, Présentation d'une pièce, J. d'urol. **16**:433-434, 1923.

4. Kretschmer, H. L.: Unilateral Fused Kidney, Surg., Gynec. & Obst. **40**:360-366 (March) 1925.

stated. Patients with this condition do not usually reach old age. In three cases operations were performed for the relief of stone. In a number of cases, fixation operations were performed. Pain is one of the most common symptoms, and may be caused by the large renal mass or by coexisting lesions in the kidney. A palpable tumor is occasionally found. The ureters open normally into the bladder. The roentgen ray is the best single aid to diagnosis, especially when both catheters lead to the large mass on one side of the body. A pyelogram often shows the calices pointing toward the median line. Failure to recognize this condition may lead to an unpleasant situation. In one case the entire renal mass was removed and the patient died from anuria. In females, solitary fused kidney may be a cause of dystocia.

RENAL STONE

Rovsing [5] reported 277 cases of renal stone in which operation had been performed at the University Clinic of Copenhagen during the last thirty-one years. When a nephrolithotomy is performed, the kidney is drawn forward and the stone located and held between the thumb and index finger. The fibrous capsule of the kidney is split along the convex border and a pair of forceps forced through the parenchyma to the region of the stone. These forceps are then opened in order to permit the introduction of a second pair which grasp and remove the stone. Since this blunt method of nephrotomy has been employed, there have been no deaths from hemorrhage, nor has it been necessary to perform a secondary nephrectomy for bleeding. After a pyelotomy is performed, the renal pelvis is sutured with catgut in two layers; the mucous membrane is not included in the sutures. In both pyelotomy and nephrotomy a cigarette drain is inserted below the lower pole of the kidney; thus the kidney is kept in its place and the formation of postoperative movable kidneys prevented. Nephrectomy is performed without opening the kidney. In forty-four (40.3 per cent.) of 109 cases of nephrolithotomy, there was a recurrence; fifty-eight of these were aseptic cases of which only fifteen (25.8 per cent.) recurred. Nephrolithotomy was performed for twenty-seven patients with infected urine; ten (37 per cent.) had recurrence. Nineteen (79 per cent.) of twenty-four patients with micro-organisms decomposing urea had a recurrence. There were only seven cases of pelviolithotomy, and in two of these the disease recurred. Nephrectomy was performed in thirty-two cases. In eighteen (58 per cent.) the pyuria and infection disappeared after the operation. In four cases nephrectomy was performed because of sterile

5. Rovsing, C. M.: On Infection as a Cause of Recurrence Following Operations for Kidney Stone, Acta chir. Scandinav. **57**:387-395, 1924.

hydronephrosis; in fourteen cases on account of pyonephrosis without decomposing micro-organisms, and in fourteen because of pyonephrosis with decomposing micro-organisms. Sixty-eight per cent. of all recurrences are found in infected kidneys, while only 53 per cent. of the recurrences are sterile.

[ED. NOTE.—Rovsing emphasizes the type of organism in relation to the type of operation to be performed. A kidney not infected with micro-organisms decomposing urea should not be drained. Nephrectomy is indicated in cases of unilateral infection with bacteria that decompose urea. The basis for the choice of operation for renal stones is the careful bacteriologic examination of the urine from the involved side. The statistics of recurrence of stone reported by Rovsing comprise a series of cases in which operations were performed over a long period, and in many cases during the formative period of urologic surgery. It is interesting to compare these results with those in a series of cases more recently reported by Braasch and Foulds. Recurrence followed in forty-four (11.8 per cent.) of 375 patients after pelviolithotomy, twenty-five (24 per cent.) of 104 patients after nephrolithotomy, and two (4.1 per cent.) of forty-eight patients after combined nephropelviolithotomy.]

Marion [6] tries medical treatment for patients who have renal colic with negative roentgen-ray findings or small shadows. If the pyelogram is negative, tuberculosis or "hydronephrosis pseudolithiasique," should be considered. If at operation a renal stone is found, nephrotomy permits exact exploration of the kidney, while pelviotomy is attended with the danger of overlooking further small stones. If the roentgen ray shows a stone shadow, then the choice of operation depends on the general condition of the patient; whether the stones are unilateral or bilateral; the kind of stones dealt with; the character of the catheterized urine, and the differential functional test of the kidneys. Marion warns against any kind of operation on patients who are in poor condition or old. In cases of bilateral stone with extensive bilateral infection, any type of operation may be fatal. In certain cases it may be necessary to operate because of pain, fever, closed pyonephrosis or similar conditions; the operation should then be done with spinal or local anesthesia.

For small renal calculi conservatism and expectant medical treatment is urged, as they frequently pass. If the stone shadows enlarge or infection is progressive, then operation is indicated. With simultaneous stones in kidney and bladder, the stone should be removed from the kidney first, as there is danger of ascending pyelonephritis or the stone

6. Marion, G.: Indications opératoires dans les calculs des voies urinaires. J. méd. franç. **12**:443-450, 1923; abstr., Ztschr. f. urol. Chir. **16**:80-81, 1924.

may pass to the bladder if the bladder is treated first. If stones are bilateral, the side most diseased should be operated on first, as any complication, such as progressive suppuration or postoperative hemorrhage, which might lead to secondary nephrectomy will leave the better kidney undisturbed. If there are stones in the kidney and ureter on the same side, the stone in the ureter should be removed first, as fistula or closed pyonephrosis may occur from obstruction of the ureter.

Pyelotomy, in these cases, is the operation of choice. The incision may be extended into the renal parenchyma if the stone penetrates the calices. Contraindications to pyelotomy are suppuration, a short renal pedicle in fat patients, or peripyelitis. If a stone corresponding to the roentgen-ray shadow is not found, then the pelvis should be incised and the pelvis and calices palpated directly with the finger or with a metal searcher. The combination of pyelotomy and nephrotomy can be employed through a small incision in case of a stone obscurely placed in a calyx or in the parenchyma. Extensive pyelotomy is reserved for cases in which there is suppuration or in which there are stones in the parenchyma and also in the pelvis. The danger of postoperative hemorrhage or suppuration is emphasized.

Nephrectomy is indicated when there is extensive destruction of the kidney (the function of the other having been found good), when there is progressive infection, and when the condition of the patient demands rapid operative procedures. Nephrostomy must be employed if the patient has only one kidney, if there is bilateral lithiasis, and if both kidneys are severely infected and function is poor. In cases of pregnancy the foregoing methods may be employed up to the sixth month. Marion recommends the removal of ureteral stones by catheter dilatation and the injection of cocain solution, fulguration of the ureteral meatus, and so forth. If these methods fail (they should not be persisted in too long), then ureterotomy by the lumbar, iliac or vaginal route should be done. In cases of anuria, after determining the site of the stone, nephrostomy or ureterostomy is indicated. In cases of pyonephrosis, after a renal functional test, the kidney should be opened and drained. In cases of hydronephrosis, the stone is first removed and nephrectomy performed later if necessary. In cases of stone in the kidney and ureter, and of destroyed kidney, nephrectomy may be performed and the ureteral stone left alone. However, if the kidney seems to have potential function, the stone is removed and later the ureteral stone. If several stones in the ureter lie close together all are removed at one time, if possible.

[ED. NOTE.—The foregoing is a good summary of the prevalent views concerning the handling of urinary calculi. To preserve the maximal amount of secreting renal tissue, with good drainage to clear

up the stone forming infection is the principle involved. The problem of bilateral calculi, especially if recurrent and if there is simultaneous impairment of renal function, is a weighty one. There is a tendency to conservatism in cases of the bilateral "stag-horn" calculi type, as many of the patients live a fairly long time with little pain and fair function, whereas operation frequently means further destruction of renal parenchyma and sometimes induces severe infection and necrosis of tissue.]

Ratschitch [7] says that urinary lithiasis, like echinococcus, occurs quite frequently in Dalmatia. He considers that a poor dietetic condition, an excess of alcoholic beverages and a sedentary life are responsible for the frequency of stone formation. The urine of most such patients is generally concentrated, strongly acid and contains many crystals of uric acid, calcium oxalate and amorphous salts. He had operated for renal stone in sixty-seven cases since 1914; in fourteen pelviolithotomy was performed; in eight nephrolithotomy; in two combined pelvionephrolithotomy, and in forty-three nephrectomy. This indicated a high incidence of renal destruction. Four patients died following nephrectomy; two from the anesthetic, one from uremia, and one from chronic septicemia. Twenty-four of the operations were conservative; there were two recurrences, both following pelviolithotomy. Seven of the thirty-nine patients living following nephrectomy had stones in the remaining kidney. Twenty-eight had clear, normal urine; eleven had slightly cloudy urine following nephrectomy.

Rafin [8] has tabulated a series of cases of renal stones in reference to the various types of operations.

1. *Operative Mortality.*—In cases of pyelotomy there were no deaths. In forty-two cases of nephrotomy, the total mortality was 9 per cent.; the aseptic cases were 11 per cent.; the infected cases, 9.5 per cent. In thirty-two cases of primary nephrectomy, the mortality was 6.6 per cent. In a large series of cases by other surgeons, Rafin found the following mortality: Pyelotomy: 1,401 cases, mortality 2.4 per cent.; nephrotomy: 1,084 aseptic cases, mortality 8.15 per cent.; 992 infected cases, mortality 13.4 per cent.; total, 10.6 per cent.; nephrectomy: 1,873 cases, mortality 8.4 per cent.

2. *Postoperative Complications; Hemorrhage.*—In one case of pyelotomy a secondary nephrectomy was performed for bleeding, and one secondary nephrectomy was performed for bleeding after nephrotomy.

7. Ratschitch, Jacques: Sur les résultats éloignés des opérations contre la lithiase rénale, J. d'urol. **18**:297-302, 1924.

8. Rafin: Valeur comparée des diverses interventions pour lithiase rénale, J. d'urol. **18**:523-524, 1924.

Cifuentes had a severe hemorrhage in eighty-five of 616 cases of nephrotomy. In thirty-six of the eighty-five cases, secondary nephrectomy was performed; twenty-two patients died.

3. *Recurrence of Stone.*—In 23 per cent. of the pyelotomy cases, in 15 per cent. of the nephrotomy cases, and in 3.3 per cent. after primary nephrectomy, there was recurrence of stone. Adding the secondary nephrectomy cases makes a total of 7.5 per cent. of recurrences.

Scheele [9] reports a case of renal stones treated by having the patient drink mineral water. The pain stopped immediately, and the stones decreased markedly in size during the next three years. The calculi having decreased in size and the kidney becoming distended and increased in size, the stones became mobile and caused obstruction, finally leading to nephrectomy.

[ED. NOTE.—There have been a number of recent reports of the dissolution of renal and vesical stones. Crowell reported a case in which disintegration of a cystin stone followed alkalization. Kindt of Copenhagen irrigated a bladder in which there was a large stone with 4 per cent. nitric acid. The stone apparently decreased in size as it was passed later. The stone was later completely destroyed in vitro with the same solution. Meyer reported cases in which stones were dissolved by constant irrigation of the bladder and the contained stones with a dilute solution of hydrochloric acid. In all these cases the procedure was controlled by cystoscopic and roentgenoscopic studies.]

Everett [10] reports the case of a woman, aged 60, who had been well until six weeks before, when, after lifting a heavy bucket of water, she had had a severe pain in her back. Six days prior to admission the pain had been severe, especially in the right side. She became quite ill with rigors and vomiting. The vomiting continued, and the pain was now in the abdomen. There were no urinary symptoms. The temperature was 99.8; the pulse was 128, and there was a rounded, tender swelling about 15 cm. in diameter, dull on percussion, in the right hypogastrium, and extending down into the right iliac fossa. Operation revealed a large perinephric abscess which was drained extraperitoneally through an anterior incision. A large stone was felt in the kidney. At the lower pole, a necrotic area was felt in the parenchyma of the kidney, where one of the projections of a large stag-horn calculus had

9. Scheele, K.: Ueber spontane Verkleinerung von Nierensteinen, Ztschr. f. Urol. **18**:528-533, 1924.

10. Everett, William: Perforation of the Kidney by a Large Branched Calculus; Perinephritic Abscess; Septicemia; Death, Brit. M. J. **1**:17-18 (Jan. 3) 1925.

penetrated. The stone was removed by nephrotomy, and the patient died on the third day. The probable sequence in the condition was stone formation, infection and necrosis of the kidney, probably six weeks prior to admission, then perforation with extravasation into the perirenal fat, abscess formation and septicemia.

Edwards [11] asserts that since Woollaston, in 1810, first discovered a cystin stone in the bladder of a child, approximately 117 cases have been recorded. He reports a case in a male aged thirty-six. Litholapaxy had been performed eight times for the removal of stones from the bladder. The patient had passed many small stones that were composed of pure cystin. Repeated examination of the urine at his first visit revealed no cystin. Two months later a specimen was obtained which contained crystals in abundance. This specimen was darker, more oily than the others, yielded a heavy deposit, and had a sweetish odor. On standing it developed the characteristic smell of hydrogen sulphid. Treatment should be directed toward arresting the excretion of cystin by the kidneys as a prophylactic against the formation of calculus. Diet has little effect. It has been shown that cystin by mouth has no influence on the output of cystin by the kidneys, although it increases the output of organic sulphate. Cystin is soluble in alkaline mediums; thus if the urine is kept alkaline, cystin crystals should not be found. Edwards feels that a conservative operation in his case would be unjustifiable, as the infection in the pelvis would again cause the formation of new stones.

RENAL TUMORS

Keynes [12] found records in the literature of only sixty squamous cell tumors of the renal pelvis. He reported three other cases. The first was that of a man, aged 35, who had been in good health up to a few months before admission to the hospital. At this time he complained of pain in the right side of the abdomen with hematuria and some frequency of micturition. By the aid of roentgen-ray and cystoscopic examinations, a diagnosis was made of pyonephrosis with stone and nephrectomy was performed. The operative findings seemed to confirm the diagnosis; however, soon after the patient left the hospital a swelling was noted in the right side of the abdomen. On readmission to the hospital some pus was evacuated from the wound, but the swelling remained. The patient died about ten weeks after the original operation.

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11. Edwards, H. C.: Cystinuria with Calculus Formation, Brit. J. Surg. **12**:345-350 (Oct.) 1924.

12. Keynes, Geoffrey: Squamous Celled Carcinoma of the Renal Calix, Brit. J. Surg. **12**:224-231 (Oct.) 1924.

On reexamination of the kidney removed at operation, a small area of typical squamous cell carcinoma was found.

The second case was that of a man, aged 54, who had had hematuria for three months and severe pain in the lumbar region for two months. Examination revealed a tumor in the left side of the abdomen; the left kidney was functionless. A left nephrectomy was performed. The kidney was an enormously distended hydronephrotic sac with a squamous cell carcinoma in the upper pole.

The third case was that of a young man of 20 with left renal pain and hematuria. The left kidney was enlarged and a diagnosis of hydronephrosis was made. On removal the kidney was hydronephrotic, but there also was an area of ulceration and leukoplakia. This case is interesting as it was an earlier stage of the condition found in the second case.

Scholl and Foulds [13] report five cases of squamous cell tumor of the renal pelvis. Squamous cell changes in the urinary tract, as in the mouth, gallbladder and other organs, generally take place in response to repeated mechanical trauma or to chronic infections. All parts of the urinary tract are subject to these changes. Metaplasia occurs both as physiologic and pathologic processes in response to trauma to tissue over an extended period of time. Not infrequently in the renal pelvis, as in the urethra and bladder, the same factor which produces metaplasia continues its action until malignant changes develop. Most squamous cell growths are preceded by leukoplasia. Squamous cell tumors of the renal pelvis are comparatively symptomless. Unlike papillary tumors they rarely bleed. Slow painless obstruction and pelvic distention occur. As with infection and stone formation, so tumor growth is often seen in abnormally developed and poorly drained kidneys. There are two types of squamous cell tumors arising in the renal pelvis: in the first, the renal parenchyma is invaded early, the kidney is solid and compact, and the parenchymal tissue becomes completely replaced by carcinoma and irregular masses of fibrosis; in the second, the growth is confined to the renal pelvis, the kidney is extremely large and hydronephrotic with a pressure atrophy of most of the renal tissue.

In the first type the carcinoma at times extends to the pedicle and neighboring glands; the pelvis is thickened and fixed by the tumor, and not infrequently stones are associated. The long duration of symptoms of calculi and infection in most cases indicates that the presence of stone may precede the development of carcinoma by many years. The malignant changes set in later, possibly as a result of long continued

13. Scholl, A. J., and Foulds, G. S.: Squamous Cell Tumors of the Renal Pelvis, Ann. Surg. **80**:594-605 (Oct.) 1924.

trauma, either inflammatory, mechanical or both. In an occasional case there is a definite increase in the severity of the symptoms, suggestive of the onset of malignancy. In the second type of squamous cell carcinoma arising in the renal pelvis, there are numerous masses on the thickened, dilated pelvic wall, some small and papillomatous, others large and bulky, and at times smooth surfaced. This type of growth causes comparatively few localizing symptoms. Metastasis occurs early and extensively in both types of squamous cell growth. In an occasional case it spreads through the blood vessels similar to the mode of extension in cases of hypernephroma. The prognosis in these cases is poor. Because of the absence of symptoms the disease is usually well advanced before the patient seeks relief. Five cases of squamous cell tumors of the renal pelvis were observed at the Mayo Clinic between 1907 and 1922. Four were associated with renal stone; the calculi in three were extremely large and of the stag-horn type. One patient died eight days after operation; three others died during the first four months. The fifth patient is alive without symptoms of recurrence six months after operation.

RENAL CYSTOMA

Antelawa [14] reports a case of fibrolipomyochondro-osteocystoma in a 2 year old child. The tumor involved the entire left renal region and histologically appeared to arise from the renal capsule. Such tumors are rare. The author reports several from the literature. As a rule prognosis is poor, the tumor diagnosed late, and operation, for this reason, unsuccessful.

RENAL PAPILLOMAS

Day [15] reports two cases of papilloma, one of the ureter and one of the renal pelvis. In the first case, the ureter was removed with the kidney and was filled with a soft papillomatous growth, which arose from the ureteral wall in many places. The kidney itself was a large dilated shell containing fragments of papillary material, none of which was attached. The patient had no trouble following the operation. The second case was a papillary tumor of the renal pelvis giving evidence of malignancy. There was a secondary chronic nephritis. Hematuria is very common in such cases, and is usually the first clinical manifestation of papilloma of the ureter. It has been noted in about 70 per cent. of the cases of tumors of the ureter. Sometimes there is associated

14. Antelawa, N.: Beitrag zur Kenntnis der retroperitonealen Mischgeschwülste der Nierenkapsel (Fibro-lipo-myo-chondro-osteo-Cystom), Ztschr. f. urol. Chir. **15**:131-136 (March) 1924.

15. Day, R. V.; Fairchild, F. D., and Martin, H. W.: A Plan for the Early Diagnosis and Management of Primary Papilloma of the Ureter and Kidney Pelvis, Surg., Gynec. & Obst. **40**:485-492, 1925.

papilloma of the bladder, due to the engrafting of small bits of tissue from the primary tumor. Sometimes tufts of papilloma may be seen protruding from the opening of the ureter. Hydronephrosis is common. Pain is usually persistent and concomitant with obstruction. It may be dull and distressing and quite pronounced in the thigh or sacral region. Day advises ureteronephrectomy in these cases. The ureter is removed quickly and easily through a comparatively small additional incision and with little or no added risk if done at the same time as nephrectomy. Secondary ureterectomy is likely to be a rather difficult operation, requiring a long incision and entailing much difficulty in dissecting out the upper ureter from the scar. Primary nephro-ureterectomy offers the maximal chance of complete cure. In the removal of a neoplastic kidney or any kind of tumor, the growth should be split and examined before closure.

RENAL INFECTIONS

Hertzler [16] divides the acute infections of the kidney into three groups:

1. Acute hematogenous infection. In this type the bacteria in the blood stream lodge in the kidney.

2. Pyelonephritis, in which both the kidney and its pelvis are involved. The acute infection probably arises primarily in the kidney and the symptoms are due to the renal lesion; the lesions in the pelvis of the kidney are secondary and subsidiary.

3. Ascending infections. In this type the infection ascends to the ureter, probably from some lesion in the lower genito-urinary tract.

In favor of the hematogenous route is the fact that bacteria circulating in the blood escape through the kidneys. In some cases of general infection of the blood, multiple abscesses may occur in the kidney. Bacterial infection in the blood stream frequently causes infection in the kidney which may travel up the ureters, but this is not common. The same type of infection occurs in the upper and in the lower urinary tract.

The kidney infected by means of the blood stream is usually intensely bluish red and may be double the normal size or even larger. It is soft to the touch with areas of firmer tissue. After the hyperacute stage is past, the kidney becomes smaller and firmer and elevated areas of grayish red are seen. In the ascending type of infection the kidneys are smaller, firmer and lighter in color; the lesions are less conspicuous, being generally more deeply seated. There may be tiny abscesses scattered throughout the kidney; these predominate, however, in the cortex. In typical cases of hematogenous infection, there is usually a chill followed

16. Hertzler, A. E.: Acute Localized Infection of the Kidney, Surg., Gynec. & Obst. **40**:247-255 (Feb.) 1925.

by high fever coming on in a patient previously healthy. The pulse remains low and there is a high leukocyte count. There is usually tenderness above the region of the kidney. The more acute, general symptoms sometimes subside after a few days, but may persist many weeks. The urine may be normal.

In secondary infections the clinical symptoms are similar but are likely to be lost in the major pyemic process. In ascending types of infection the lower urinary symptoms precede the infection of the kidney. The hematogenous type may require operation. In the secondary type any local treatment is usually useless; and in the ascending type, which is bilateral, operative treatment is of no value unless there are perirenal abscesses. Hertzler concludes that hematogenous lesions of the kidney are, in most instances, not abscesses but infarcts; various types of pyelitis are secondary to infections of the kidney of hematogenous origin, and the chief factor in their treatment is the eradication of the source of infection. Ascending infection of the kidney has not been proved. The site of the lesion indicates that bacteria in the urinary tract gain entrance to the blood stream and pass by this avenue to the kidney. The difference in the character of the lesions is due to the difference in the offending organisms.

RENAL TUBERCULOSIS

Smirnoff [17] examined the uninvolved portion of twenty-two tuberculous kidneys and found a nonspecific change in the areas remote from the tuberculous nodes in eighteen. These changes consisted of an inflammatory process in the region of the malpighian bodies, a type of glomerulonephritis. The author believes that this nephritis is probably due to the excretion of the toxins of tuberculosis. Similar changes have been repeatedly cited by other authors in cases of pulmonary tuberculosis that have come to necropsy. Federoff, in 1922, reported four cases of typical renal tuberculosis in which there were leukocytes and the bacilli of tuberculosis in the urine, but on removing the kidneys no specific changes were found. It is believed that tuberculosis can produce a nonspecific nephritis in the kidney without producing the usual pathologic picture of caseous renal tuberculosis. The glomeruli, the tubules or the vessels and interstitial tissues may be involved, separately or together. This may lead ultimately to a contracted kidney. The renal tuberculosis may begin with such nephritis. The process may go on to the stage of contracted kidney or may result in the development of tuberculous nodes and the usual picture of renal tuberculosis.

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17. Smirnoff, I.: Zur Frage der kochobacillären Nephrocirrhose, Urologiia **1**:7-12, 1923; abstr., Ztschr. f. urol. Chir. **16**:76-77, 1924.

[ED. NOTE.—The excretion of bacteria by the kidneys without anatomic demonstration of renal disease is well known and, as Smirnoff mentions, this may be true likewise of the bacillus of tuberculosis. However, the demonstration of the bacilli tuberculosis in the urine is usually enough to make the diagnosis of renal tuberculosis almost certain, and the cases described in which anatomic tubercles cannot be found under such circumstances must be very exceptional.]

Suter [18] reports the results in 204 cases of renal tuberculosis in which operation was performed between 1896 and 1920. Five patients (2.5 per cent.) died within the first six weeks, one from hemorrhage, one from paralytic ileus and parenchymatous nephritis, one from tuberculosis peritonitis, one from thrombophlebitis of the femoral artery, and one from thrombophlebitis and pulmonary tuberculosis. Of the 199 remaining patients, 192 were traced. Fifty-four, thirty-three men and twenty-one women, had died. In twenty-nine patients the remaining kidney was diseased. The average duration of life after operation of those who died was five and one-half years. Eighty-one per cent. of the men who died had genital tuberculosis. Twenty-nine died from other affections than those of the kidney; nine died from miliary tuberculosis, seven from pulmonary tuberculosis, one from spondylitis, and eight from nontuberculous conditions. Of the 138 patients living, 59.4 per cent. were entirely cured, 25.3 per cent. improved, and 15.3 per cent. were not yet improved. Women obtained a better result than men. Results from the standpoint of the operation period were: From 1896 to 1905, thirty-three patients, 57 per cent. well and 43 per cent. dead; from 1906 to 1912, sixty patients, 61.5 per cent. living and 38.4 per cent. dead. Of patients improved in 1912, 30 per cent. had died by 1920. Of patients unimproved in 1912, 100 per cent. had died by 1920. Of patients cured in 1912, 20 per cent. had died by 1920.

The condition of the bladder is of great moment in prognosis. Of those who are apparently cured, the capacity of the bladder will be at least 285 c.c.; in those who are improved but not cured, about 135 c.c., and in those who are unrelieved, it will be about 85 c.c. In cases of renal tuberculosis and pregnancy, nephrectomy is indicated if the bladder is healthy, but if the bladder is unhealthy, it is better first to interrupt the pregnancy and then perform nephrectomy. A woman on whom nephrectomy has been performed bears subsequent pregnancy well. Of eleven such patients ten remained well during pregnancy while one developed renal tuberculosis and died.

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18. Suter, F.: Bericht über 204 Nephrektomien für Nierentuberkulose, Schweiz. med. Wchnschr. **53**:1097-1101, 1923; abstr., Ztschr. f. urol. Chir. **15**:337-338, 1923-1924.

[ED. NOTE.—This analysis of end-results of nephrectomy for renal tuberculosis corresponds fairly well with that of Braasch and others in this country. The capacity of the bladder as a factor in prognosis is not a new idea, but it is a point worthy of further emphasis. It may be taken, to some extent, as an index of the extent and probable duration of the disease, as well as its pathologic virility. Suter's attitude toward nephrectomy in pregnancy, even with slight involvement of the bladder, would probably not go unchallenged in spite of the excellent statistical argument presented. Likewise, most urologists would feel safer in warning patients who have had nephrectomy for tuberculosis to avoid future pregnancy, as the gravid state may be associated with progressive extension of the tuberculous inflammation.]

GENITAL TUBERCULOSIS

Reinecke [19] reported 128 operations on ninety patients with genital tuberculosis in the St. George Krankenhaus since 1895. Reinecke believes that isolated testicular tuberculosis is rare. Probably the seminal vesicle is most frequently the first point of the genital tract to be affected. The epididymis was affected in 50 per cent. of the cases. The disease was unilateral in most cases. In only six patients was there bilateral disease early in the history. Twelve patients gave a history of trauma a few weeks before the obvious onset of the disease. Twenty-six gave a history of gonorrhea months or years before the onset of the disease. Early symptoms are fever and subjective complaints in the perineal region coincident with filling of the seminal vesicle; then the palpable, painful epididymis appears. After two or three weeks, a progressive thickening of the epididymis is noted and the pain is greatly lessened. The Wassermann and tuberculin tests, the temperature curve, roentgen-ray investigation of the lungs, examination of the urethra by palpation and by endoscopy, expression of the prostate and cystoscopy are employed in the diagnosis. It is sometimes difficult to make a diagnosis, especially in the early stages, and it may only be made at operation.

Operative results showed that of eleven patients on whom partial epididymectomy was performed, seven were traced. One had died from pulmonary tuberculosis and six had progressive genital tuberculosis. Of three patients on whom total epididymectomy was performed, all had progressive genital tuberculosis. Unilateral castration was performed on forty-nine patients. Of these twenty-one died, three were living, and the fate of twelve was not known. Of thirteen others, eight were in poor condition and had signs of tuberculosis of the lung. Three patients had had tuberculous fistulas for years; they had had operations for joint

19. Reinecke, R.: Zur männlichen Genitaltuberkulose, Deutsch. Ztschr. f. Chir. **180**:130-157, 1923; abstr., Ztschr. f. urol. Chir. **15**:203-204, 1923-1924.

or renal tuberculosis in childhood. Four patients had residual bilateral tuberculosis of the seminal vesicle.

The fact that sixteen of the forty-nine patients had recurrent or progressive residual tuberculosis with fistulas for longer or shorter periods of time is not in accord with the supposed tendency for residual nodes in the prostate and seminal vesicles to heal after castration. In twelve necropsies after unilateral castration, anatomic healing of the tuberculous tissue in the seminal vesicles could not be demonstrated. Thirteen patients with bilateral castration were observed. Four were living, eight were dead, and one was not traced. All patients with the exception of one child had seminal vesicle or prostatic disease. A radical operation was performed on one side in nine cases, with removal of the seminal vesicle. Unilateral conservative operations had previously been performed in all. One patient died three and one-half years after operation from genital tuberculosis; one died one month after operation from infection and bleeding; the remainder were in good health from one to three years after the operation. Reinecke recommends a vasotomy on the opposite side after unilateral operations to prevent transmission of tuberculosis from the male to the female in coitus.

[ED. NOTE.—The foregoing represents a poor outlook in general for patients with genital tuberculosis. The fact that seven of nine patients did well after seminal vesiculectomy supports the contention of Young, who has been advocating more radical surgical extirpation of the diseased areas in genital tuberculosis, rather than conservative epididymectomy.]

RENAL TUBERCULOSIS

Wallner [20] studied forty cases of genital tuberculosis treated surgically in the Jena surgical clinic from 1911 to 1920. He concluded that epididymectomy or semicastration should be performed, each having its sharp limitations. If the epididymis alone is demonstrably involved, then epididymectomy is to be done, especially if patients are under 50 and if there is no sign of testicular reaction, such as hydrocele. If before or during the operation the testicle is demonstrably diseased, then the operation of semicastration is indicated. An exploratory incision may be made at the time of operation, but the healing of small tuberculous nodes is less likely than the further caseation of the testis, and castration will probably be necessary later. Semicastration is always indicated for elderly patients. It is a moot point whether with disease of one epididymis and the prostate and seminal vesicles, one should not resect the vas deferans of the other side, especially in patients who are

20. Wallner, Adolf: Zur Klinik der männlichen Genitaltuberkulose, Ztschr. f. urol. Chir. **15**:137-163, 1923-1924.

under 50. The bilateral disease of elderly patients is treated by total castration. If patients are young, it may be well to leave a part of the testicular tissue on the less diseased side, particularly at the first operation. Later it may be necessary to remove all the tissue.

Associated prostatic and seminal vesicular tuberculosis should be treated surgically only occasionally, if at all. It is difficult to draw conclusions as to operative results as "one can only see what one has removed and not what one has left behind." In other words, it is difficult to diagnose the extent of the disease at the time the patients come for treatment. With extensive tuberculosis elsewhere, surgical measures should be used cautiously, heliotherapy or radiotherapy being carried out.

[ED. NOTE.—In spite of the wide publicity given to the etiology, mode of spread, and the treatment of genital tuberculosis, knowledge concerning it advances slowly. Whether the prostate, vesicle or epididymis is the primary focus is not known. Young's contention that radical surgical extirpation of seminal vesicles and vas should be done in such cases is theoretically sound, but such procedures have not been generally adopted. Certain surgeons believe that such an extensive operation might open up fresh avenus for the invasion of the bacillus tuberculosis. Wallner found the results most satisfactory in cases in which an early diagnosis was made and unilateral operation performed early. This experience has been almost universal, and leads to the thought that general facts concerning epididymal tuberculosis have not been taught. The problem has the same phases as that of cancer, that is, early diagnosis, early extirpation and cure.]

Nitch [21] has reviewed the subject of renal tuberculosis. The disease is one of unusual interest because of the two distinct clinical varieties, which we call medical and surgical, respectively. In the medical form the disease is bilateral, infection is nearly always hemic, there is coexistent parenchymatous nephritis, the urine contains the bacilli tuberculosis, albumin of sanguineous origin and hyaline and granular casts. Physical signs of chronic nephritis in the form of edema with arterial and cardiac changes are often present, and death from uremia is not uncommon. The actual tubercles are scattered irregularly throughout the cortex and medulla, the greatest number being in the cortex, but, as has been pointed out, although tubercles are often limited to the cortex, they are seldom found in the medulla without a cortical lesion. In the surgical form the disease is unilateral at the beginning. Infection follows the blood or lymph stream; the urine is cloudy or turbid and contains the bacilli tuberculosis, pus cells, caseous material, fragments of renal tissue, phosphates, red blood corpuscles and albumin of pyogenic

21. Nitch, C. A. R.: Renal Tuberculosis, Lancet **1**:1-10 (Jan. 3) 1925.

origin. The focal lesions are limited in number and undergo caseation and liquefaction, forming an open or closed tuberculous abscess. The pathologic anatomy is similar in its essentials to that of the medical form, but differs in degree. Bilateral surgical tuberculosis is practically always secondary to a primary unilateral infection, which, if allowed to persist for a sufficient length of time, will spread to the lower urinary tract and slowly but surely reach the opposite and once healthy kidney.

European writers have estimated, from an enormous number of cases, that bilateral surgical infections should not exceed 15 per cent., but more recently Braasch has shown by animal inoculation that in seven out of twenty-two cases, apparently unilateral, the opposite side was infected. He has shown further that after removal of an obviously diseased kidney patients have signs of active urinary tuberculosis. These results indicate that our conception of an apparently unilateral lesion may require reconsideration.

In the past there have been considerable differences of opinion with regard to the route by which the bacilli of tuberculosis reach the kidney, but now there are only two channels which need be considered, the blood vessels and the lymphatics. A careful study of the pathologic anatomy of the disease makes it clear that a primary infection is nearly always carried through the blood stream. It is hardly necessary to point out that the term "primary infection" is not scientifically correct, for the bacilli must have originated in some tuberculous focus, most probably a tuberculous mediastinal gland, but it signifies that the kidney has been infected from a quiescent and obscure lesion. Nitch accepts Halle's pathologic classification which includes: (1) primary closed parenchymatous tuberculous nephritis; (2) primary open tuberculous pyelitis or pyelonephritis, and (3) a combination of these two.

The diagnosis depends on the symptoms of vesical irritation and acid, turbid, sterile urine containing pus cells, the bacilli of tuberculosis, and occasionally blood in varying amounts. Given these data the site of the lesion is determined by cystoscopy.

The treatment of unilateral renal tuberculosis can be summed up in three words, early lumbar nephrectomy. The kidney should be removed with its capsule and any perinephric fat which is adherent to it. When dense adhesions render subcapsular enucleation necessary, the results are unsatisfactory and the operation is likely to be followed by a persistent tuberculous sinus. If the disease is complicated by a perinephric abscess, nephrectomy must be deferred until the abscess has yielded to treatment. The kidney must never be incised to verify a diagnosis which should have been complete and certain before operation, since the surrounding tissues will be infected and the wound may take months to heal. After operation a prolonged course of tuberculin

should be given. Nitch, while admitting that the results of the surgical treatment of renal tuberculosis are not as good as they should be, believes that when the medical profession as a whole has learned to regard all cases of mild "cystitis" with suspicion, and when the ureters of a patient with a sterile purulent urine are regularly catheterized and the two specimens of urine are examined for bacillus of tuberculosis, there will be a negligible operative mortality, a great increase in the percentage of cures, and a corresponding diminution in the troublesome genito-urinary complications.

Wildbolz [22] describes a type of tuberculous nephritis in which there is no definite focus of tuberculosis. This condition, which is very similar to the fibrous form of renal tuberculosis, is rarely associated with typical tuberculous tissue destruction.

[ED. NOTE.—Wildbolz has become an authority of note on renal tuberculosis. His book on the subject discusses all phases of the condition. Tuberculous nephritis is not uncommon in one kidney in association with extensive tuberculous destruction of the opposite kidney. This condition is responsible for an occasional death following the removal of the more definitely diseased kidney. In several cases at necropsy, after the removal of one tuberculous kidney, definite nephritis and only a few small, fibrous tubercles were found in the remaining kidney.]

Martin [23] outlines a regimen for the treatment of renal tuberculosis, the chief factors of which are diet, heliotherapy, diathermy, hydrotherapy, hygiene and rest. An attempt is made to afford maximum nourishment, and at the same time impose the minimum of elimination on the kidneys. Foods rich in calcium and iron salts are particularly selected, also bulk is provided to combat intestinal stasis. Heliotherapy is employed in the form of direct sunlight and air baths and also by the use of the Alpine light. This treatment is used as a preoperative procedure to protect the patient from a flare up, and also postoperatively as an aid to the healing of sinuses and for the relief of vesical symptoms.

NEPHROSTOMY OF REMAINING SIDE

Verrière,[24] in three advanced cases of tuberculosis of the bladder with simultaneous tuberculosis of the kidneys (one side being completely

22. Wildbolz, Hans: Tuberkulöse Nephritis und Nierentuberkulose, Ztschr. f. Urol. **18**:566-571, 1924.

23. Martin, W. F.: Physiotherapy in Renal Tuberculosis, J. Urol. **12**: 493-501 (Nov.) 1924.

24. Varrière: Quelques cas de néphrostomie unilatérale pour cystite douloureuse après néprectomie ou exclusion spontanée de l'autre rein, J. d'urol. **16**:433, 1923.

destroyed), performed nephrostomy on the most favorable side. This was done because the other kidney was beginning to show signs of insufficiency. The results in the three cases were satisfactory. At the end of two and one-half years one was alive and able to work. In a fourth case, a neoplastic tumor of the bladder caused great pain. After extirpation of one contracted kidney, nephrostomy was performed on the other side. After six months the kidney showed good function and the patient seemed much improved. Nephrostomy or ureterostomy is therefore recommended in suitable cases.

[ED. NOTE.—It is the usual experience that nephrostomy and ureterostomy lead to infection, stasis, and impairment of renal function. In the cases mentioned, the function seems to have been maintained for a considerable time after operation. In certain cases the procedure is justified as palliation.]

(To be continued.)